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Original Articles

Clinical Observations before and after Mitral Valvuloplasty: Physical, Radiologic and Electrocardiographic Changes 995
John F. Otto, Jr., J. Morrison Hutcheson, Jr., Walter H. Abelmann, Dwight E. Harken, John E. Gary and Laurence B. Ellis

Absorption of Radioactive Vitamin B_{12} in Nonanemic Patients with Combined-System Disease 1005
Irwin M. Arias, Leonard Apt and Myron Pollycove

Acute Hemolytic Anemia, Cryoglobulinemia and Cold Agglutination: Report of a Case 1011
Harold O. Conn

Acute Vascular (Schönlein–Henoch) Purpura — an Immunologic Disease? 1014
Marshall B. Kreidberg, William Dameshek and Rocco Latorraca

Medical Progress

Emergence of Antibiotic-Resistant Bacteria (Concluded) 1019
Maxwell Finland

Medical Intelligence

Acute Suppurative Parotitis: Report of Two Cases 1028
Lt. Colonel Edwin J. Pulaski and Major William M. Keeling

Case Records of the Massachusetts General Hospital . 1030

Editorials

"Groundedly Learned" 1039
Resistance of Bacteria to Antibiotics . . . 1040
Association on Alcoholism 1041
Plastic-Pecking Pigeons 1041

Massachusetts Medical Society 1042
Civil Defense Agency 1044
Notices 1048
Massachusetts Department of Public Health . . 1047
Correspondence 1047

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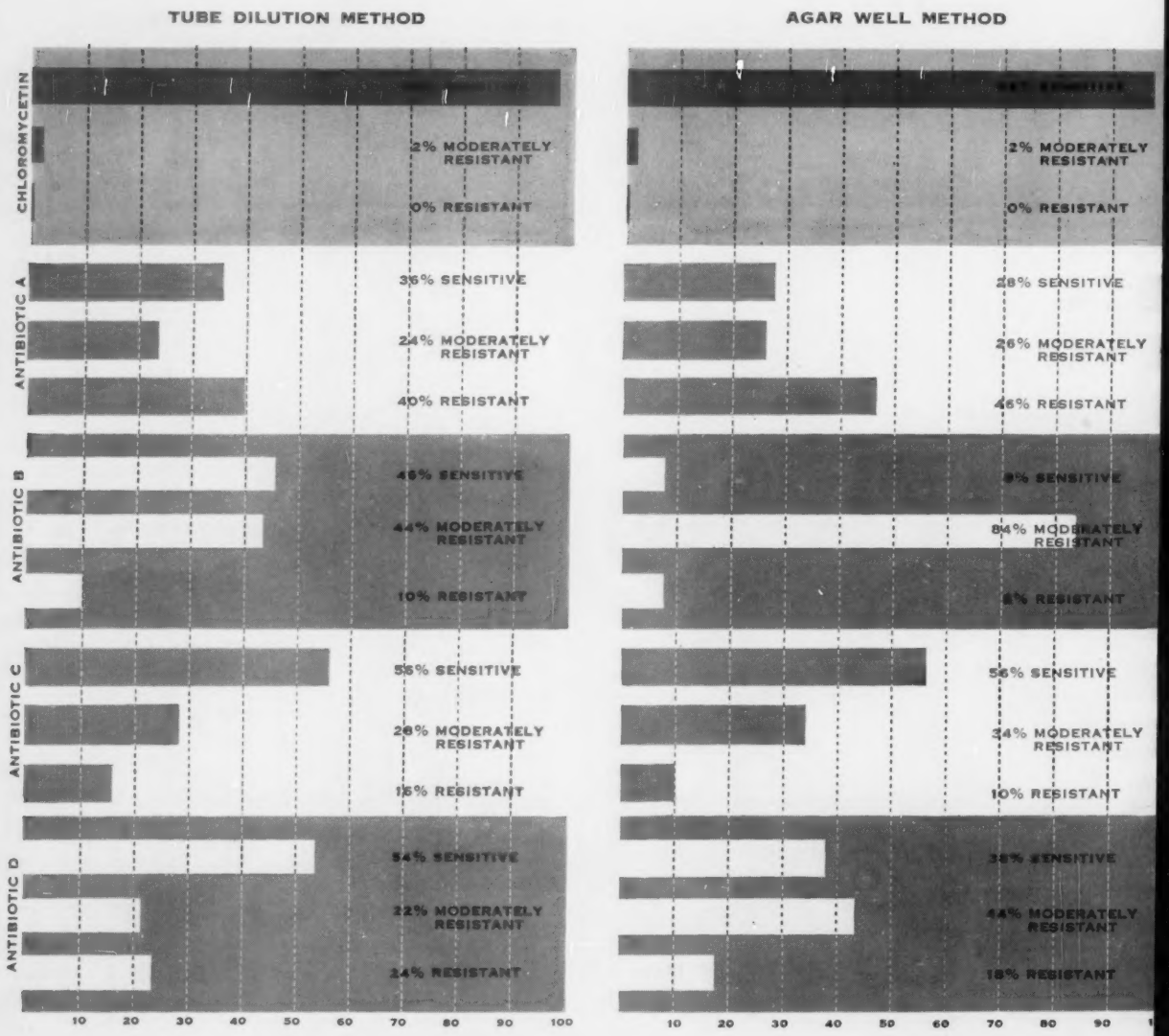

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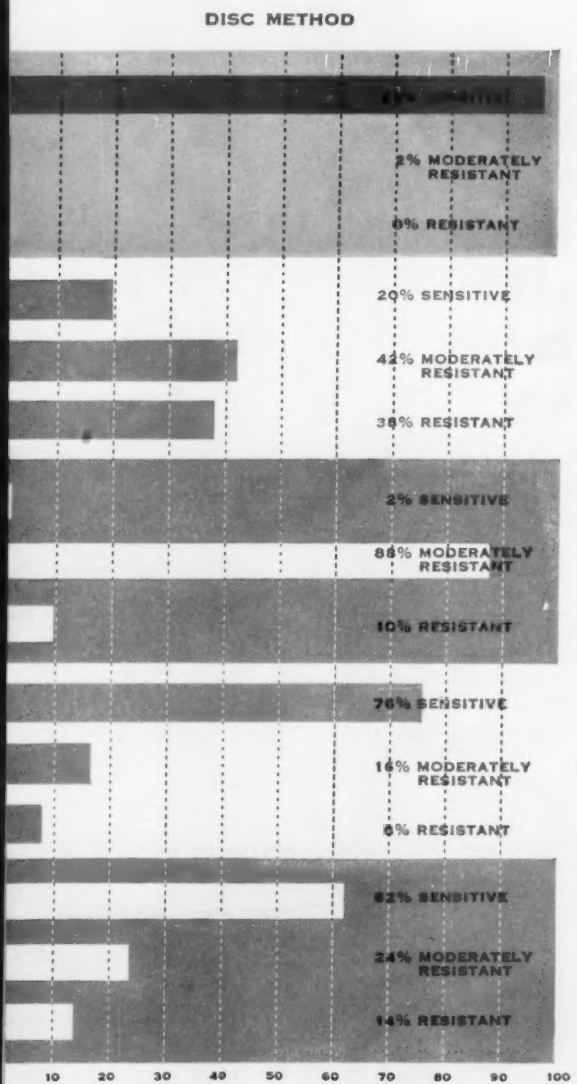

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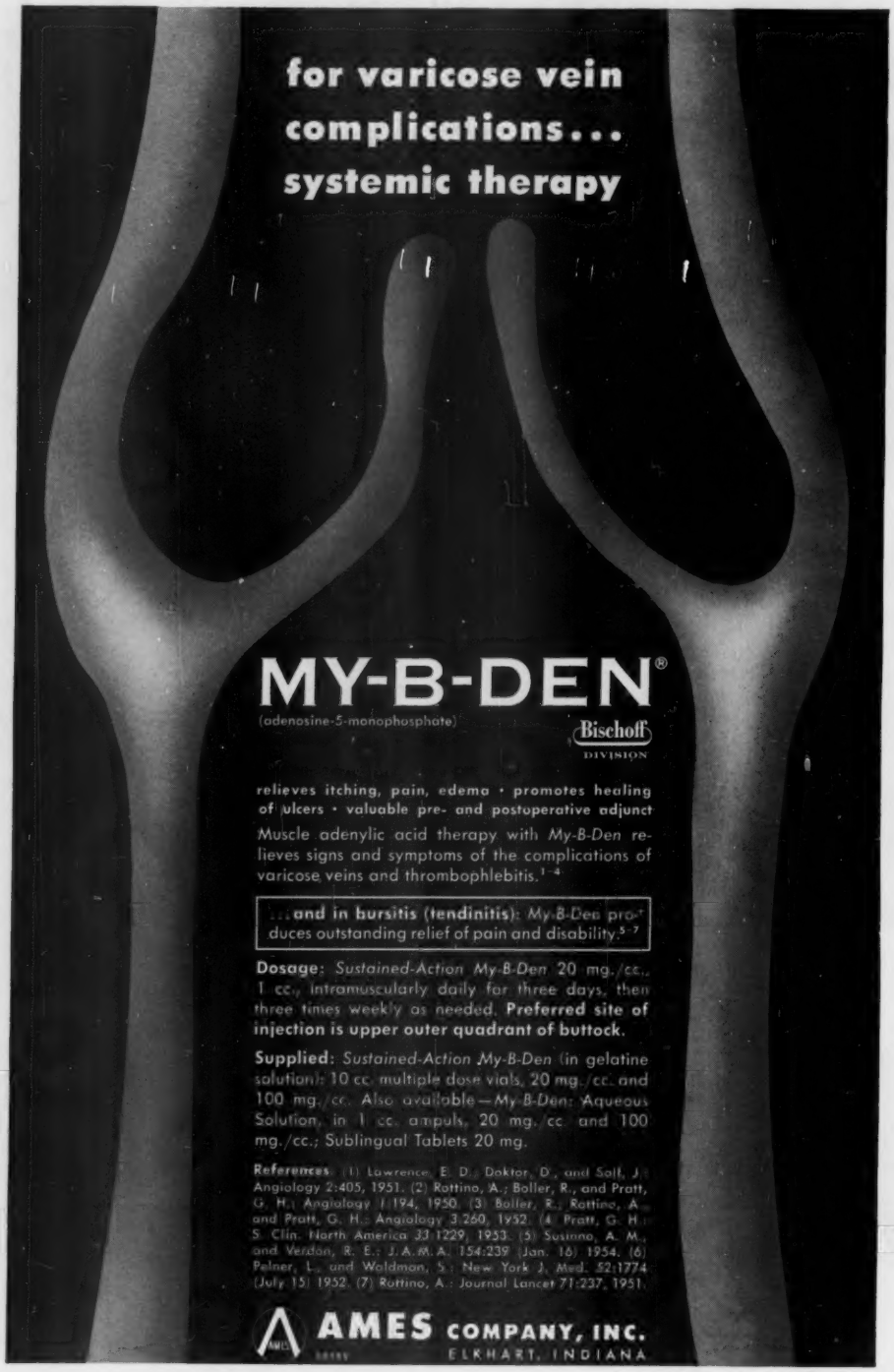
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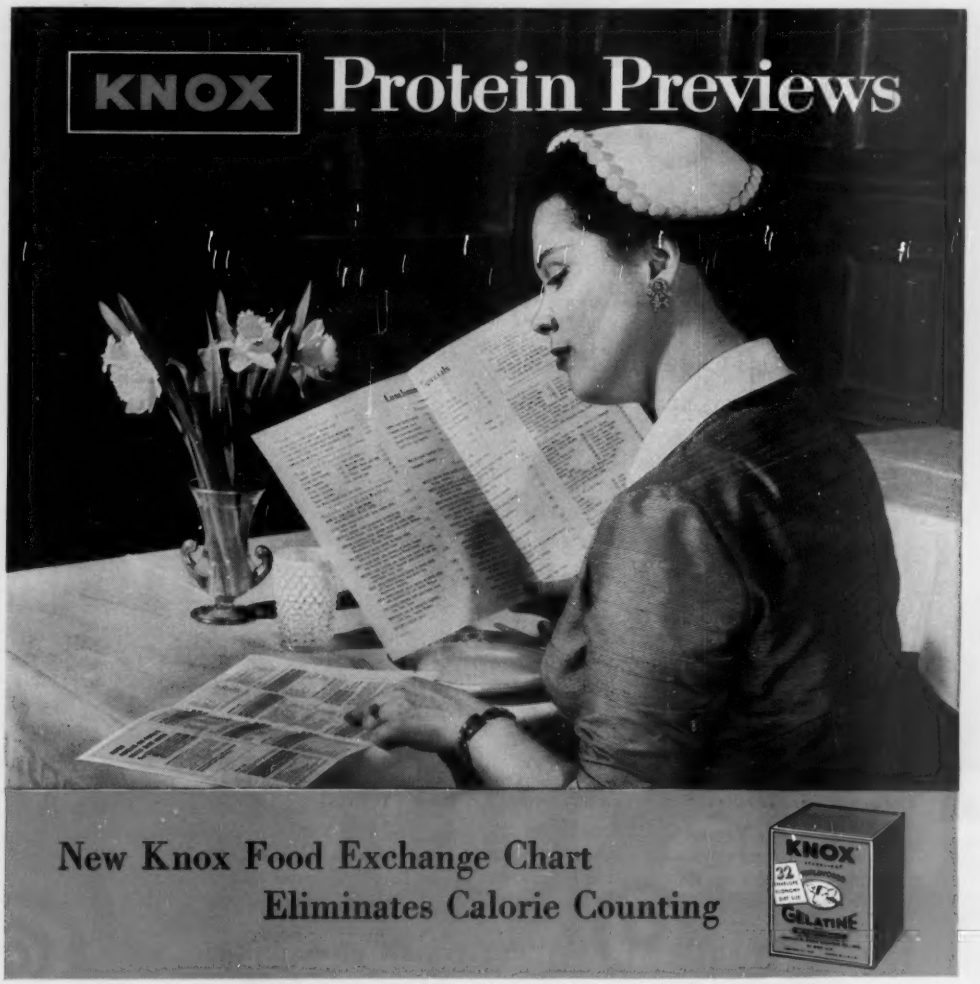

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Fig. 1.—Above, photomicrograph of T. vaginalis organism six seconds after contact with 1:250 solution of Carlendacide. Below, photomicrograph of organism 12 seconds after contact with solution.

after contact with a 1:250 solution of Carlendacide (fig. 2 and 3). Owing to the presence of blood serum or agar in the culture mediums, contact with some flagellates on a slide is delayed, but in our tests all have been killed

as drinking water solution as drinking water group had ; 255 gm.) more th

Clinical Trials. Carlendacide in t who had T. vagi effort was made t week, two the sec patient did not re and night, using a lendacide to a qu fice treatment c Miller speculum, lints, drying the ring forceps, the solution of Carle ments suggested

TABLE 2.—*Effectiv* Volunteer

Lauryl sulfate and Lauryl sulfate wit

Alkyl aryl sulfona Alkyl aryl sulfonat

Polyoxyethylene m Polyoxyethylene no

cleansing of the ulum, it should b since it cannot douche once or period and then days before the infection is lim to eliminate all of treatment; he

6. Davis, C. H., ease of Trichomonas 304, 1954.

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Bibliography

1. Davis, C. H.: J.A.M.A. *157*:126 (Jan. 8) 1955. 2. Davis, C. H.: Am. J. Obst. & Gynec. *68*:559 (Aug.) 1954. 3. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 1955. 4. Davis, C. H.: J.A.M.A. *92*:306 (Jan. 26) 1929.

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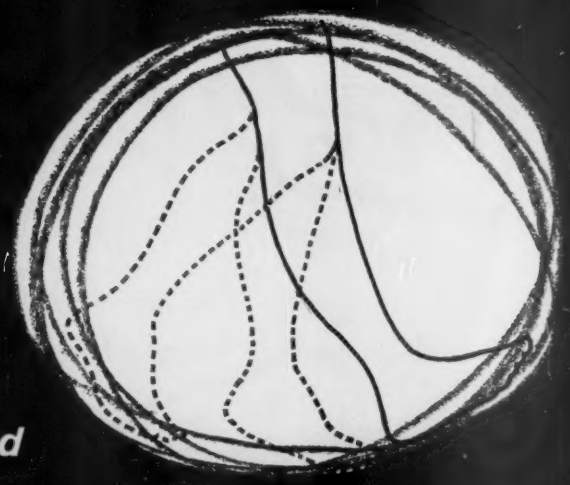

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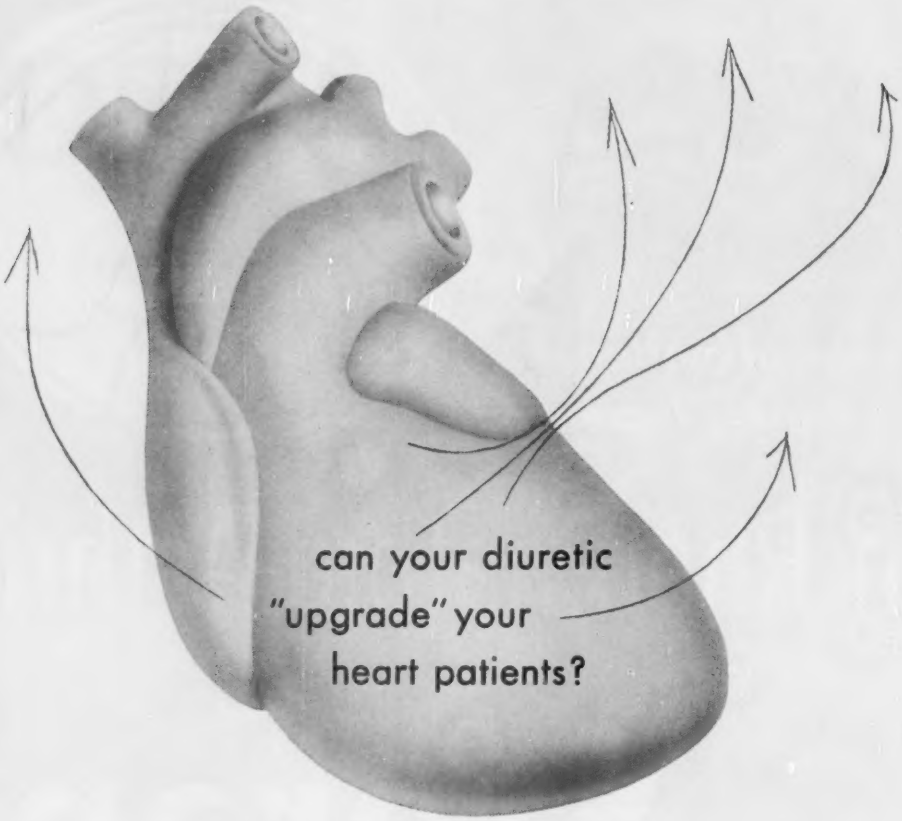

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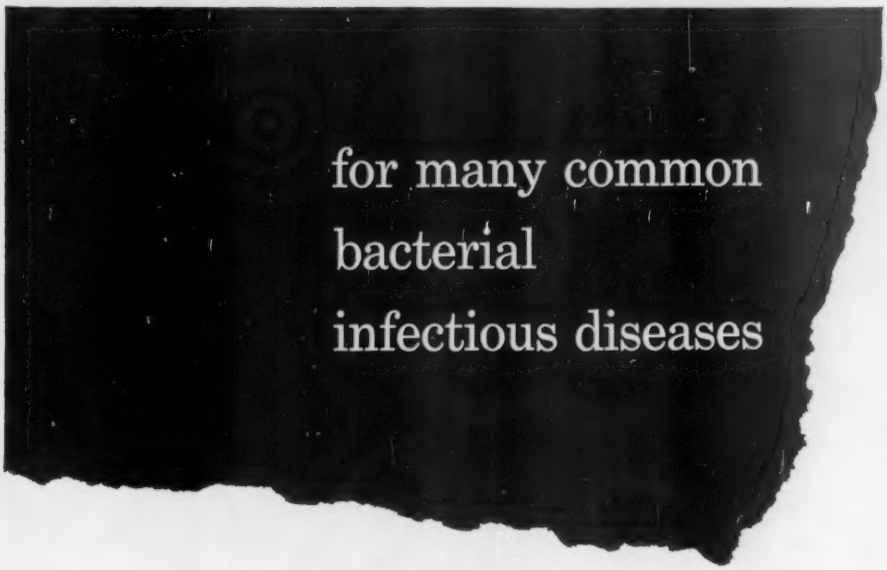

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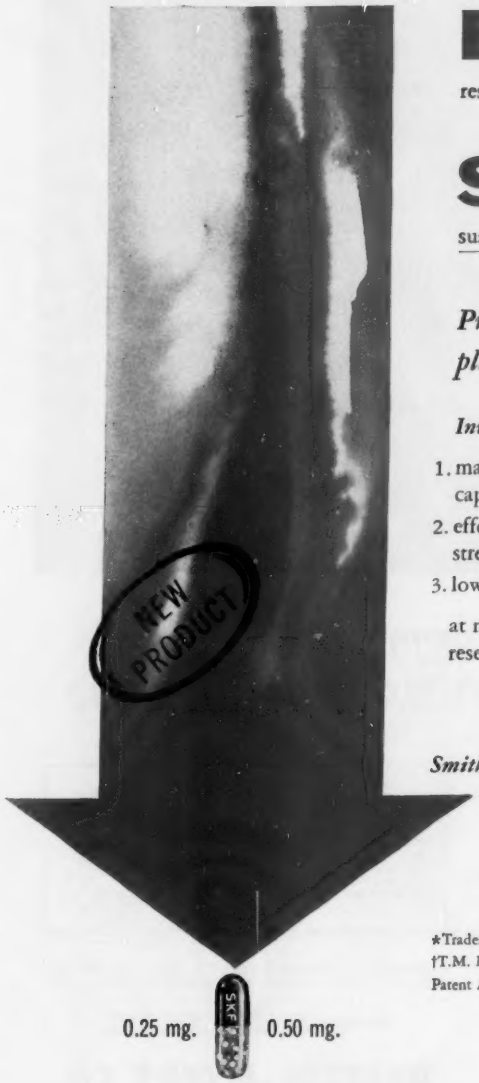

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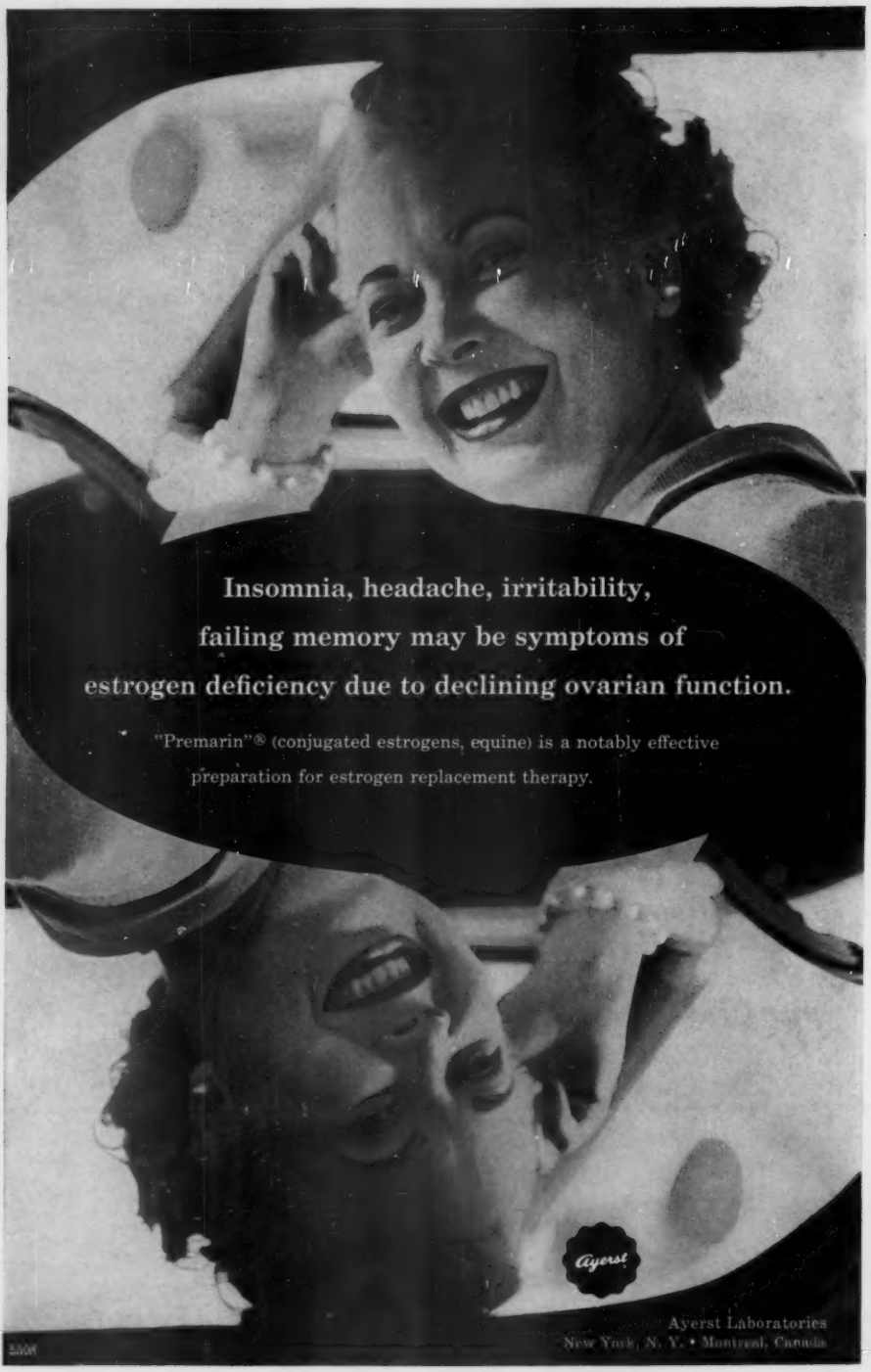
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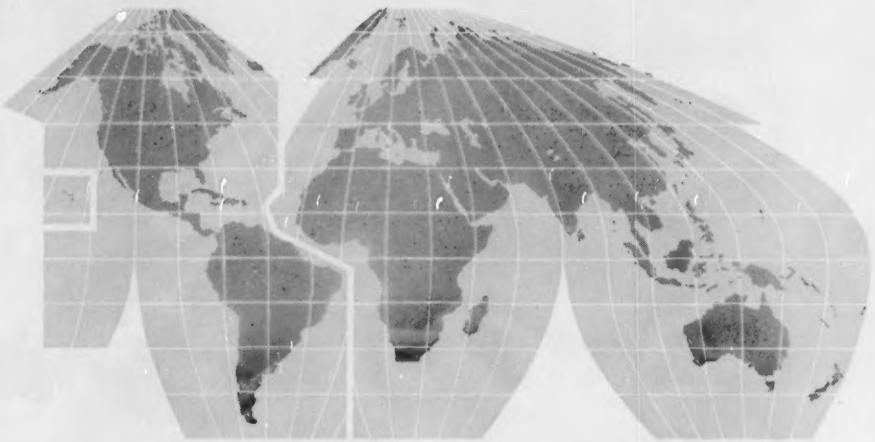

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Volume 253 DECEMBER 8, 1955 Number 23

CLINICAL OBSERVATIONS BEFORE AND AFTER MITRAL VALVULOPLASTY*

Physical, Radiologic And Electrocardiographic Changes

JOHN F. OTTO, JR., M.D.,† J. MORRISON HUTCHESON, JR., M.D.,† WALTER H. ABELMANN, M.D.,‡ DWIGHT E. HARKEN, M.D.,§ JOHN E. GARY, M.D.,¶ AND LAURENCE B. ELLIS, M.D.‖

BOSTON

OPERATIVE correction of the stenotic mitral valve has become an established surgical procedure during the past seven years, and is being performed with increasing frequency. Much has been learned about the indications for surgery, the surgical technics, the operative risks and complications, and the symptomatic improvement to be expected in properly selected patients. Much remains to be learned, and certain misunderstandings persist. It should be remembered that the scarred, deformed and often calcified mitral valve cannot be transformed into a normal structure even though its function may be improved. Furthermore, there are factors besides the anatomic deformity that contribute to the eventual postoperative result. Consequently, certain physical findings or other objective criteria of heart disease are likely to persist despite marked symptomatic benefit, although signs closely related to the disordered physiologic state may show amelioration. This clinical study was undertaken to clarify these points.

MATERIAL AND METHODS

One hundred and thirty-two consecutive patients surviving operation were chosen. All had a preoperative diagnosis of predominant mitral stenosis without important associated disease of the valve. Five had died before follow-up study, and 21 were not available, so that 106 returned for this follow-up study and constitute the material for this report. The selection of these patients, out of a total experience of about 900 patients with mitral stenosis operated on by one of us (D.E.H.) was based on the fact that the operations were all performed at the Boston City Hospital or Mount Auburn Hospital and that the patients all lived within a 200-mile radius of Boston. The operative results in those who did not report for follow-up examination, according to questionnaire analysis, did not differ from the remainder.

There were 30 males and 76 females, a sex distribution that confirms the known predilection of pure mitral stenosis for women. The preoperative classification of patients has been discussed previously,[1] and the distribution in this series is presented in Table 1.

The interval since operation varied from twelve to fifty-six months, and the mean follow-up period was twenty-four months. At the time of follow-up study, a careful interval history was obtained from each patient, the degree of disability was estimated as objectively as possible, the functional capacity was rated according to the criteria of the New York Heart Association, and the degree of symptomatic improvement was compared with the preoperative state according to the following scheme: markedly improved, moderately improved, slightly improved, unchanged or worse. Each patient had completed a detailed questionnaire before the follow-up examination, and the degree of disability determined by analysis of the written answers was compared with that determined by personal interview. These two methods of evaluation agreed closely, as reported elsewhere.[2] The percentage of patients who improved in this group did not differ from that of the larger group of 440,[2] of which the present series forms a part. It was concluded that this series was a representative sample of the entire group in terms of preoperative disability and symptomatic benefit.

At follow-up study, the results of physical examination, cardiac fluoroscopy and electrocardiography

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were recorded and compared with the preoperative data. All murmurs were graded in intensity from 1 to 6 according to the criteria of Levine and Harvey.[3] Although cardiac fluoroscopy was performed in every case before and after operation, the analyses of radiologic changes were limited to 54 patients in whom the fluoroscopy was performed on both occasions by the same radiologist (J.E.G.). The clinical data were not available to the radiologist. Special technics were used to assure reproducible positioning of the patients so that preoperative and follow-up films and heart measurements could be compared reliably.[4] An over-all evaluation of the radiographic changes was obtained by a blind technic, in which the postero-anterior, lateral and oblique films before and after operation were compared on two separate occasions, and the total change was rated as "none," "improved" (+1 to +3) or "worse" (−1 to −3).

Table 1. *Distribution of 106 Patients by Functional Group.*

Group*	Preoperative Classification	Postoperative Classification
	No. of patients	No. of patients
1	0	44
2	3	41
3	80	21
4	23	0

*Group 1: patients without significant symptoms.
Group 2: patients handicapped by some symptoms but able to carry on sedentary occupation (not progressive).
Group 3: patients disabled by symptoms, mainly pulmonary, but able to do light housework or its equivalent (in preoperative group symptoms progressive).
Group 4: cardiac invalids, mostly in chronic congestive heart failure or requiring strict antidiuretic regimen.

Standard 12-lead electrocardiograms were obtained, and all measurable data were recorded. Electric axis was estimated to the nearest 5 degrees from limb and unipolar leads. The diagnosis of incomplete right-bundle-branch block was made in the presence of an rSr′ in Lead V_1, occasionally in Lead V_3R or V_2, in association with a delay in onset of the intrinsicoid deflection of more than 0.04 second. The criteria for the diagnosis of ventricular hypertrophy were those of Sokolow and Lyon.[5,6]

Symptomatic Improvement and Change in Treatment

Fifty-six per cent of the group under consideration were estimated to be markedly improved, 21 per cent were moderately improved, 20 per cent were only slightly better, and 3 per cent were unchanged. Thus, 77 per cent of the patients living at least a year after operation had definitely worthwhile improvement.

For the purpose of rating improvement, the most valuable criterion was the change in general level of activity of the patient. This required close questioning and analysis of occupation, recreation and all every-day living habits by which tolerance for exertion could be semiquantitatively measured. The functional capacity was closely related to exertional dyspnea and, to a lesser extent, to fatigue. A number of other symptoms or events were evaluated in the over-all estimate of clinical benefit, including orthopnea, paroxysmal dyspnea, true pulmonary edema, cough, hemoptysis, palpitation (tachycardia or arrhythmias), chest pains, embolic phenomena and edema or other manifestations of frank congestive heart failure.

Within limits the postoperative medical regimen reflected the clinical state. The reduction in therapy was most apparent in the group with more advanced disease (Table 2). Thus, of those who required diuretics of various types before operation, 70 per cent now receive less or none. Almost 40 per cent of the patients who restricted their sodium intake now eat more salt, and most of these take essentially normal diets. Of course, many improved patients continued to limit salt intake as a matter of custom rather than necessity. Half the patients with normal sinus rhythm who took digitalis for some months or years before operation have discontinued the drug entirely. It has been customary to keep all persons with atrial fibrillation on a maintenance dose of digitalis.

Improvement may continue for many months. Although most of the increase in functional capacity occurred during the first six months, the majority of patients continued to improve at a slower rate during the second six-month period, and a few did not achieve maximal subjective benefit until two years or more after the operation. This improvement has been maintained during the follow-up period in the great majority of patients, but a few have regressed. When regression did occur it usually took place within two years of the operation. The loss of symptomatic improvement after months or years is a complex subject, and one that will receive analysis in a subsequent report. It is pointed out below that the regression could be expected in some patients, that it was to some extent predictable, and that it usually seemed to be related to factors besides active rheumatic carditis.

Table 2. *Change in Treatment after Valvuloplasty.*

Therapy	No. of Patients	Decrease in Therapy	No Change in Therapy	Increase in Therapy
		No. of patients	No. of patients	No. of patients
Diuretics	63	44	18	1
Sodium restriction	92	36	56	0
Digitalis (all patients)	92	30	59	3
Digitalis (patients in normal sinus rhythm)	64	30	34	0

Body Weight

The mean edema-free preoperative body weight of the female patients was 54 kg. (119 pounds), and the average weight at the time of follow-up examination was 57.2 kg. (126 pounds). The corresponding figures for the male patients were 63 kg. (139 pounds) and 65.8 kg. (145 pounds) respectively. These relatively small increases obscure the fact that a third of the patients gained from 4.5 kg. to 14.5 kg. (10 to 32 pounds), or 7.7 kg. (17½ pounds) on the average. This weight gain accompanied general symptomatic improvement during the year after operation; it was most likely to occur in women and in patients who had been underweight and in those whose symptoms were greatly improved.

Blood Pressure

The average blood pressure was 117 systolic, 72 diastolic, preoperatively and 129 systolic, 76 diastolic, at the time of follow-up study. Although statistical analysis of the mean systolic difference was not justified, the increases in systolic and pulse pressures of some patients were quite striking: systolic pressure rose 20 mm. or more in 26 per cent, and pulse pressure increased by 20 mm. or more in 20 per cent.

Fifteen per cent of the patients in this series had preoperative systolic blood pressure between 90 and 100; none of them had significant mitral regurgitation at the time of operation, and the systolic pressures in this group rose an average of 14 mm. No correlations were found between pulse pressure and palpable valve size or regurgitation.

In 2 women in this series arterial hypertension has developed since operation. In 1 of these, the progressive increase in systolic blood pressure for several months after operation suggested that the hypertension had been masked by tight mitral stenosis.

Auscultatory Findings

Apical Diastolic Murmurs

Only 1 patient had no diastolic murmur audible before operation, and in this case the murmur became audible after surgery. The murmurs were usually louder in patients with sinus rhythm, as compared to those with atrial fibrillation. This distinction was probably largely a function of the prominent presystolic component in hearts with normal rhythm.

There was a tendency for the diastolic murmurs to become less intense after surgical treatment. The changes were usually not marked, however, and the murmur completely disappeared in only 10 per cent of the cases. The mitral diastolic murmur was somewhat more likely to diminish in patients showing great clinical improvement (Table 3). Although the murmur may decrease in the immediate postoperative period,[7] this has been of no value in indicating the eventual prognosis in the individual case.

The presystolic component and duration of the murmurs were not sufficiently well differentiated in this study for their changes to be analyzed separately. The frequent relation between mitral incompetence and diastolic murmurs of short duration,[8] however, was confirmed by their occurrence together in 15 patients in this study. The postoperative changes in diastolic murmurs may be more marked if the presystolic component is evaluated separately.[8] It was our experience that all portions of the murmur tended to diminish.

Apical Systolic Murmurs

An apical systolic murmur was heard in slightly more than a third of the patients before operation,

Table 3. *Change in Intensity of Mitral Diastolic Murmur in Relation to Postoperative Class and Symptomatic Improvement.*

Postoperative Class*			Change in Murmur†	Symptomatic Improvement		
1	2	3		Marked	Moderate	Slight or None
%	%	%		%	%	%
64	55	43	Decreased	60	57	42
36	35	43	No change	38	29	46
—	10	14	Increased	2	14	12

*New York Heart Association classification of functional capacity.
†Percentage of patients in each group.

and three fourths of the murmurs were of Grade 1 or 2 (Table 4). These murmurs were more frequent in patients who had palpable mitral regurgitation at the time of operation, and 6 out of 8 patients with Grade 3 murmurs had such regurgitant jets. Of the 2 Grade 3 apical systolic murmurs that were not associated with palpable mitral incompetence, 1 was probably transmitted from the tricuspid area, and the other, which was of short duration in systole, disappeared after surgery. There were only 2 patients with Grade 4 apical systolic murmurs; both had palpable mitral regurgitation, and both were only slightly improved by correction of the stenotic component.

Apical systolic murmurs of Grade 1 and 2 were associated with palpable mitral regurgitation in 15 cases, and occurred in 13 patients without insufficiency. Despite the low intensity of the murmur, other clinical data led to the preoperative clinical diagnosis of mitral insufficiency in 11 of the 15 cases in which it was surgically found, whereas this diagnosis was suggested in only 2 of the other 13 with equivalent murmurs. Significant mitral regurgitation was usually suspected on the basis of other criteria, even though the apical systolic murmur was slight.

The absence of an apical systolic murmur was good but not infallible evidence against serious mitral regurgitation. In a fifth of the patients who had no apical systolic murmur some degree of palpable re-

gurgitation was found at operation, but this was usually mild. This comprised a third of the patients with palpable mitral regurgitation; all these patients improved significantly except the 1 with a marked regurgitant jet, whose improvement was slight.

Apical systolic murmurs as well as mitral insufficiency were more common in patients with more advanced heart disease, in terms of disability, over-all heart size and frequency of atrial fibrillation.

The postoperative changes in the apical systolic murmurs were unpredictable and were not well correlated with the surgical impression of the residual anatomic defect. Of the 14 patients in whom palpable mitral regurgitation was not associated with a preoperative apical systolic murmur, a murmur became audible after valvuloplasty in 8. Of 6 cases in which palpable regurgitation appeared or increased after valve fracture, the apical systolic murmur became louder in 3, but remained unchanged or decreased in the other 3. Of 8 patients in whom the regurgitant jet disappeared or diminished after fracture and mobilization of the leaflets, 4 had no murmur before or after the procedure, 3 had murmurs that increased in intensity, and only 1 had a murmur that became softer. Thus, surgical estimates of regurgitation had little relation to changes in these murmurs.

Although 61 per cent of the preoperative murmurs were associated with palpable regurgitation, only 48 per cent of the postoperative murmurs could be thus explained. This is related to the larger number of postoperative systolic murmurs that could not be correlated with operative findings, since an existent apical systolic murmur decreased or disappeared after surgery in 15 patients, whereas the murmur increased or made its appearance in 32. The net effect was more frequent and louder murmurs in the postoperative group. The development of a postoperative systolic murmur in this series had no prognostic significance.

TABLE 4. *Apical Systolic Murmurs in 106 Cases of Mitral Stenosis in Relation to Palpable Mitral Regurgitation.*

MITRAL REGURGITATION	NO MURMURS	GRADE 1 MURMURS*	GRADE 2 MURMURS*	GRADE 3 MURMURS*	GRADE 4 MURMURS*	TOTAL PATIENTS WITH MURMURS
	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	
Before operation:						
Present†	14	7	8	6	2	23
Absent	55	6	6	2	0	14
After operation:						
Present‡	12	2	11	6	4	23
Absent	46	6	11	7	1	25

*Criteria of Levine & Harvey.[3]
†Palpable jet before valvuloplasty.
‡Palpable jet after valvuloplasty.

TABLE 5. *Other Murmurs in 106 Cases of Surgically Treated Mitral Stenosis.*

TYPE OF MURMUR	NO. OF CASES BEFORE OPERATION	DECREASE OR DISAPPEARANCE OF MURMUR	NO CHANGE IN MURMUR	INCREASE OR 1ST APPEARANCE OF MURMUR
		NO. OF CASES	NO. OF CASES	NO. OF CASES
Parasternal diastolic	39	18	21	2
Basal systolic	34	21	11	9

Other Murmurs

A parasternal diastolic murmur, which was usually high pitched, blowing and of low intensity, was often heard in early diastole along the left sternal border. Because of its soft quality it is easily missed, and its true prevalence is difficult to judge. Such a murmur was described in 37 per cent of the patients before and in 26 per cent after operation. It decreased or disappeared in almost half (Table 5) and did not change in the remainder; it was first heard after surgery in only 2 patients.

It was usually impossible to be sure whether this murmur represented disease of the aortic valve or functional pulmonary insufficiency, although the latter was more often thought to be the explanation and disease of the aortic valve was questioned seriously in only 8 of 39 cases. This functional origin was partially confirmed by the tendency of the murmur to diminish, and by the fact that the murmur was rarely heard in the absence of readily demonstrable dilatation of the pulmonary artery. There was no correlation between this murmur and electrocardiographic findings, clinical state or prognosis.

Fifty-nine per cent of the preoperative parasternal diastolic murmurs were associated with soft basal systolic murmurs. This murmur was usually maximal in the pulmonic area, but occasionally was louder just to the right of the upper sternum. The basal systolic murmur was seldom of aid in this series in establishing the presence of aortic-valve involvement, since it often seemed to be of functional origin. The 2 murmurs tended to occur together, and the systolic

murmur showed a similar tendency to diminish after surgery. Thus, of 34 such basal systolic murmurs audible before operation, 21 (62 per cent) decreased or disappeared, and only 2 became louder.

First Mitral Sound

In 93 patients the quality of the heart sounds was recorded, and in all but 3 the first mitral sound was accentuated preoperatively. Of these 3, all had some palpable mitral regurgitation at operation, 2 had atrial fibrillation, and 2 had loud systolic murmurs as well. The importance of the accentuated first mitral sound in distinguishing stenosis from incompetence has been established.[8]

There were 12 patients in whom an accentuated first mitral sound returned to normal after operation. Of these 12, 9 were greatly, and 2 moderately improved by the surgical procedure. The patient with only slight improvement was one in whom mitral regurgitation, produced surgically, could have accounted for the dampened first heart sound. Half our patients showed some reduction in the intensity of the first sound. This was more likely to occur in those with marked clinical improvement and diminution in the diastolic murmur, and could not be related to the surgical production of mitral regurgitation. This reduction in intensity was not always apparent in the immediate postoperative period[7,9] but more commonly occurred as a gradual process over a period of many months.

Second Pulmonic Sound

Accentuation and reduplication of the second pulmonic sound was noted in 84 out of 92 patients.

TABLE 6. *Teleroentgenographic Cardiac Measurements before and after Valvuloplasty.*

MEASUREMENT	NO. OF OBSERVATIONS	AVERAGE BEFORE OPERATION*	AVERAGE AFTER OPERATION†
		cm.	*cm.*
Transverse diameter	53	13.7±1.8‡	13.9±1.7
Long diameter	52	15.6±1.3	15.4±1.3
Broad diameter	52	11.6±1.0	11.6±1.1
Esophagosternal distance	41	11.3±1.6	11.0±1.9

*Cardiothoracic ratio in 53 observations 52.2 per cent±7.0.
†Cardiothoracic ratio in 53 observations 52.6 per cent±7.0.
‡Standard deviation of mean.

Three of the 8 with no increase in the sound were only slightly improved, and 4 cases had palpable regurgitation at operation. In none were electrocardiographic signs of enlargement of the right ventricle present; there were no significant shifts in electric axis or rotation after surgery, and the pulmonary-artery enlargement tended to be slight. The second pulmonic sound is an important though not completely reliable guide to the degree of pulmonary hypertension present.[8] A diminution in the intensity of this sound after operation occurred in a third of our patients, with a return to normal in 17 per cent. The second pulmonic sound seldom changed very much in the immediate postoperative period,[7,9] but it did show a distinct tendency to diminish in subsequent months.

TABLE 7. *Roentgenologic Changes in 54 Patients Twelve to Thirty Months after Valvuloplasty.*

HEART CHAMBER OR VESSEL	DECREASE IN SIZE	NO CHANGE IN SIZE	INCREASE IN SIZE
	NO. OF CASES	NO. OF CASES	NO. OF CASES
Main pulmonary artery	12	35	7
Peripheral pulmonary vessels	19	23	12
Right ventricle	12	32	10
Left atrium	16	31	7
Left ventricle	1	52	1
Heart & great vessels (over-all)	22	15	17

RADIOLOGIC FINDINGS

Heart Measurements

When teleroentgenographic cardiac measurements were averaged, there was no difference between the preoperative and follow-up groups in over-all heart size (Table 6). When the individual cases were analyzed to detect those with alteration in general heart size by these criteria, only 9 per cent showed a decrease in the cardiothoracic ratio of 10 per cent or more, and 6 per cent an increase of similar magnitude. These changes bore no relation to improvement by other criteria, since the 3 patients whose cardiothoracic ratio increased all had considerable clinical improvement, and of the 5 patients whose transverse heart size decreased by a similar amount, 1 was clinically no better, and 4 received marked benefit.

Heart Chambers and Pulmonary Vessels

Changes in size of the individual heart chambers and pulmonary vessels are presented in Table 7, which includes some chambers of normal size preoperatively that could not be expected to become smaller. In 49 patients who had distinct preoperative enlargement of either the right ventricle or the main pulmonary artery, one or both of these structures became smaller in a third but enlarged in a fifth. The peripheral pulmonary vessels were enlarged before operation in 47 cases; 40 per cent appeared smaller, and 21 per cent larger at the time of follow-up examination. The left ventricle appeared to change its size in only 2 patients; in 1 of these, who had slight mitral regurgitation at operation, it became slightly larger, and in the other a slight preoperative enlargement disappeared.

Relation of X-Ray Findings to Clinical Improvement

The over-all radiologic changes are correlated with symptomatic improvement in Figure 1, in which the line connects the median of each group. Although the overlaps are large, it can at least be said that most of the patients showing x-ray improvement also

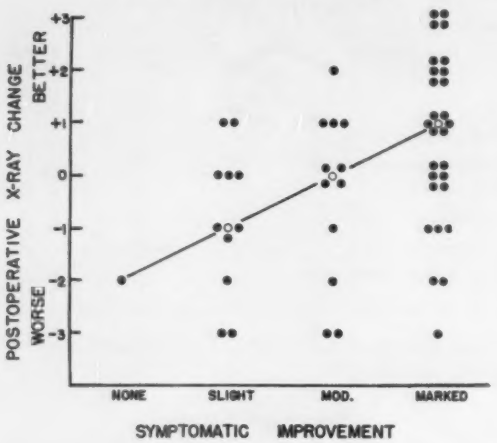

FIGURE 1. *Relation of Over-All Postoperative Radiologic Changes to Symptomatic Improvement.*

received great symptomatic benefit. In relatively few of the markedly improved patients did the over-all x-ray findings change for the worse.

Patients with radiologic evidence of deterioration were in a prognostically more unfavorable group, in that they had more factors known to affect adversely the long-term results (Table 8). Thus, these patients were usually over forty years of age and had mitral-valve calcification; they were more likely to have mitral insufficiency and a wide mitral aperture at the time of operation, and more often had atrial fibrillation. There was no evidence, however, that active rheumatic carditis was involved in this group; only 7 of the 17 patients with postoperative radiologic deterioration had shown Aschoff bodies in the atrial appendages removed at operation—a rate of occurrence that did not differ from that found in the entire surgical series.[10] Five of the 17 patients in this unfavorable group have shown some symptomatic regression, after obtaining maximal improvement during the first postoperative year or two, compared to only 1 out of 22 in the group in whom the x-ray appearance had improved. If this trend is confirmed in a larger series, the over-all radiologic impression will be of prognostic value in evaluating the likelihood of persistent functional improvement.

X-Ray Diagnosis of Mitral Insufficiency

Five of 51 patients in whom satisfactory fluoroscopic data were available were thought to have mitral regurgitation by the criterion of systolic expansion of the left atrium. Of these 5 only 1 had palpable regurgitation at operation. Of 12 patients who were found to have a regurgitant jet at the time of surgery, only 1 had been thought to have mitral incompetence by fluoroscopy. It is clear that these fluoroscopic findings were of no value in the diagnosis of mitral insufficiency. The pitfalls in the use of this diagnostic criterion have been discussed previously.[11]

Valvular Calcification

A radiologic diagnosis of calcification of the mitral valve was made in 16 out of 53 cases before surgery, and was confirmed at operation in all 16. There were an additional 4 cases in which calcified valves were palpated at operation, and in 2 of these the calcification was detected at postoperative radiologic examination. Thus, there was good correlation between radiologic and palpable evidence of calcification: palpable mitral calcification had been predicted on x-ray study in 80 per cent of the cases before and was seen in 90 per cent after operation. There were no cases in which calcium was visible but not palpable.

It has been found that mitral insufficiency is more frequent in patients with heavy calcification of the valve, so that this finding may be of prognostic as well as diagnostic importance. Out of 258 patients with palpable mitral calcium operated on by one of us (D.E.H.), 48 per cent had some degree of mitral incompetence at the time of surgery, and this increased to 57 per cent after completion of the valve fracture.[12] Of 276 patients without gross mitral calcification, 17 per cent had palpable regurgitation, increasing to 31 per cent after valvuloplasty.

TABLE 8. *Over-All Roentgenographic Changes in 39 Patients in Relation to Occurrence of "Adverse Factors."*

FACTOR	OVER-ALL X-RAY CHANGE	
	PATIENTS WORSE	PATIENTS IMPROVED
Patient over 40	10	5
Patient not over 40	7	17
Atrial fibrillation present	6	4
Atrial fibrillation absent	11	18
Bivalvular disease present	4	2
Bivalvular disease absent	13	20
Mitral regurgitation present	7	4
Mitral regurgitation absent	10	18
Preoperative valve size of 1.0 cm.	7	2
Preoperative valve size under 1.0 cm.	10	20
Valvular calcium present	11	4
Valvular calcium absent	6	18
Recurrence of symptoms	5	1
No recurrence of symptoms	12	21
Mean "factors" per patient	2.9	1.0

Electrocardiographic Findings

Rhythm

There was no significant difference in the proportion of patients with normal sinus rhythm or atrial fibrillation before and after operation. Of 43 patients with preoperative fibrillation, 4 reverted to sinus rhythm, 2 with quinidine and 2 spontaneously. Of 63 patients with preoperative sinus rhythm, 2 now have atrial fibrillation.

Atrial fibrillation was seen more commonly in the patients with greater disability and in those with palpable mitral regurgitation at the time of surgery. A somewhat smaller percentage of patients with this arrhythmia were greatly improved by valvuloplasty, as compared to patients with sinus rhythm. However, only 2 out of 43 patients with fibrillation failed to receive at least slight benefit, and 42 per cent of them were much improved.

Fewer patients in this group were markedly improved, not only because their heart disease was more advanced but also because mitral insufficiency was more frequent. In a consecutive series of 852 patients operated on by one of us (D.E.H.), 64 per cent of 249 patients with palpable mitral regurgitation at surgery had atrial fibrillation, as compared to 46 per cent of 603 patients without mitral regurgitation.[12]

Axis

The mean preoperative electric axis in 102 cases was $+80°\pm3°$, and the mean follow-up axis was $+67°\pm3°$. This reduction in axis was significant ($p<0.05$). There were only 5 patients who had axes of less than $+30°$ before surgery. A third of the preoperative patients had an axis of $+100°$ or more, whereas only 12 per cent of the postoperative group had this degree of right-axis deviation. At the time of follow-up study 43 per cent of the patients had a shift in electric axis toward the left of 20° or more, and this finding was correlated with clinical improvement (Table 9). Thus, 80 per cent of those with such a shift in axis were markedly improved, compared with 40 per cent of the remainder. Only 5 per cent showed a significant shift toward the right after surgery. As we had expected, right-axis deviation was correlated with other electrocardiographic manifestations of enlargement of the right ventricle, except that it had no relation to incomplete right-bundle-branch-block patterns.

P Waves

The majority of patients with sinus rhythm had "P mitrale," manifested by a broad P wave of normal amplitude that was flat-topped or notched. There were only 3 cases, out of 58, of classic "P pulmonale," manifested by peaked P waves of 3 mm. or more in amplitude.

The mean preoperative P-wave amplitude in 58 cases was 2.0 mm., and the mean postoperative amplitude was 1.5 mm., a difference that is not significant. However, the P wave became measurably smaller (by 0.5 mm.) in 50 per cent, and decreased by 1.0 mm. or more in 28 per cent. The higher the P wave, presumably the greater the component of P pulmonale, and the greater the tendency for reduction in amplitude. Thus, P waves of 2.5 mm. or higher in 17 patients became smaller in all but 2, and the average reduction was 1.2 mm. In each of the 3 cases of pure P pulmonale, the amplitude decreased by 1.5 to 2.5 mm. As would have been expected, P waves were significantly higher in patients with electrocardiographic manifestations of hypertrophy of the right ventricle.

Table 9. *Change in Electric Axis in Relation to Symptomatic Improvement.*

Change in Axis	No. of Cases	Marked Symptomatic Improvement	Moderate Symptomatic Improvement	Slight Symptomatic Improvement or None
		No. of cases	No. of cases	No. of cases
Shift to left of 20° or more	44	35	5	4
Others*	58	23	17	18

*Includes 53 with no significant change & 5 with shift of axis to right.

The P mitrale showed no definite alteration. The width did not change and the notching, when present, usually persisted.

PR Interval

There were 3 cases out of 61 with sinus rhythm before surgery in which the PR interval was prolonged: 0.24, 0.26 and 0.32 second. These PR intervals had all decreased to normal at the time of follow-up examination; the last 2 were associated with the omission of digitalis, and all 3 patients were greatly improved by clinical criteria. The record with the longest PR interval, 0.32 second, was associated with marked electrocardiographic signs of enlargement of the right ventricle, which showed a striking postoperative reversion to normal. There was 1 case in which the PR interval became prolonged (to 0.26 second) after surgery; this patient was unimproved by operation, and his unexplained deterioration after a brief initial benefit may have been due to rheumatic myocarditis.

Right-Bundle-Branch Block

Of 102 electrocardiograms, the pattern of *incomplete* right-bundle-branch block was noted in 29 per cent before surgery, and in 27 per cent at follow-up study. Although this pattern had disappeared in 9 cases at the time of follow-up examination, it appeared after operation in 7, so that the preoperative and postoperative rates of occurrence were much the same.

The pattern of incomplete right-bundle-branch

block was not intimately related to other electrocardiographic evidence of enlargement of the right ventricle. Thus, it occurred in the absence of other electrocardiographic signs of that diagnosis in the majority of cases, and it was present in only half the preoperative cases with an electrocardiographic diagnosis of hypertrophy.

There was no distinct correlation between the presence of incomplete right-bundle-branch block and fluoroscopic size of the right ventricle or pulmonary artery. The existence of such a pattern, in the absence of other evidence of ventricular enlargement, was not related to clinical status or to subsequent improvement.

TABLE 10. *Electrocardiographic Diagnoses of Enlargement of the Right Ventricle in 102 Cases, and Their Changes after Valvuloplasty.*

ELECTROCARDIOGRAPHIC DIAGNOSIS	NO. OF CASES BEFORE OPERATION	DISAPPEARANCE AFTER OPERATION	DECREASE AFTER OPERATION	NO CHANGE AFTER OPERATION
		NO. OF CASES	NO. OF CASES	NO. OF CASES
Definite hypertrophy of rt. ventricle	23	12	9	2
Probable hypertrophy of rt. ventricle	4	3		1
Ventricular dilatation alone	1	1		
Totals	28	16	9	3

Complete right-bundle-branch block was found before surgery in 2 patients, in 1 of whom it was intermittent. The stable block has not changed, and the intermittent one has become permanent. The symptoms of both patients were markedly improved. In addition, intermittent right-bundle-branch block has made its appearance in 1 patient in whom it was not observed preoperatively.

Enlargement of Right Ventricle

The electrocardiographic signs of ventricular hypertrophy were considered unequivocal in 23 patients and probable in an additional 4, and ventricular dilatation ("strain") alone was diagnosed in 1. On x-ray examination, each of these patients showed a large pulmonary artery with prominent branches. Furthermore, the patients whose electrocardiograms indicated marked improvement in the patterns of ventricular enlargement were also the most likely to show improvement by radiologic criteria. This was manifested most often by diminution in the size of the peripheral vessels or main pulmonary artery, and less often by a decrease in the size of the right ventricle. The electrocardiographic changes were generally more striking and probably reflected better than the x-ray findings the improvement in pulmonary hypertension.

Of the 28 patients with electrocardiographic signs of enlargement, most showed a striking change toward normal at the time of follow-up study (Table 10). Most of the difference could be accounted for by a decrease in clockwise rotation,[13] as well as a shift in axis toward the left, and frequent reversion of ST-segment and T-wave changes over the right ventricle. When the diagnostic criteria for hypertrophy were tabulated by the method of Sokolow and Lyon,[5] 27 patients had a total of 172 criteria before surgery, and 57 at the time of follow-up examination; the mean criteria per patient had been reduced from 6.4 to 2.1. The criterion of a prolonged activation time seldom showed a significant postoperative change in our cases. Patients with electrocardiographic signs of enlargement of the right ventricle, exclusive of patterns of incomplete right-bundle-branch block, were very likely to have much clinical improvement (Table 11).

Enlargement of Left Ventricle

At the time of follow-up study the development of hypertrophy of the left ventricle was suspected from the electrocardiogram in 8 patients, almost entirely on the basis of increased voltage of the R wave in Lead V_5.[6] In no case could we be confident of the diagnosis, although the diagnostic difficulties in the presence of combined ventricular hypertrophy are well known.[14] The suspicion of enlargement of the left ventricle was supported by fluoroscopic findings in 2 of these patients, although this was present to the same degree before surgery. Three of the 8 had palpable regurgitation before and after valvuloplasty. Another has hypertension, 1 probably has significant aortic regurgitation, and another has angina pectoris; only 1 of the 8 was greatly improved by valvuloplasty.

TABLE 11. *Relation of Electrocardiographic Patterns of Enlargement of the Right Ventricle before Operation to Postoperative Symptomatic Improvement.*

ELECTROCARDIOGRAPHIC SIGNS OF VENTRICULAR ENLARGEMENT	NO. OF CASES	MARKED SYMPTOMATIC IMPROVEMENT	MODERATE SYMPTOMATIC IMPROVEMENT	SLIGHT SYMPTOMATIC IMPROVEMENT OR NONE
		NO. OF CASES	NO. OF CASES	NO. OF CASES
Present	29*	24	3	2
Absent	71	33	18	20

*Includes 1 patient with preoperative pattern of hypertrophy who manifested complete right-bundle-branch block after surgery.

Enlargement of the left ventricle may become unmasked after the operation as a result of a decrease in the predominance of the right ventricle. However, of these 8 patients, only 2 showed a significant postoperative shift in the electric axis, and only 1 had an obvious change in rotation; none had had electrocardiographic signs of hypertrophy of the right ventricle before surgery.

DISCUSSION

It has been apparent to all observers that the symptomatic benefits achieved by surgical treatment of

mitral stenosis are usually more dramatic than the changes in physical or laboratory findings. The operation obviously is not curative, in that the valve structure remains distorted to a variable degree depending on the amount of fibrous or calcific thickening of the leaflets and chordae tendineae. Furthermore, the effects of the disease on the myocardium and pulmonary vessels may not be completely reversible, reversibility being related to such factors as the severity and duration of the valvular disease and pulmonary hypertension, or to the presence of rheumatic myocarditis or its results.

Nevertheless, important objective changes follow valvuloplasty, and some of these have at least a rough correlation with symptomatic benefit. The most important of these alterations are related to the reduction in pressures proximal to the stenotic valve. Catheter studies have established that elevated pressures in the left atrium and pulmonary artery can be expected to diminish. The pulmonary-artery pressure and, more importantly, the pulmonary vascular resistance may not decrease immediately, but will often fall gradually over a period of many months.[8,15] This is surely related to the frequent concomitant delay in reaching maximal symptomatic improvement. Despite known structural changes in the smaller pulmonary arterial vessels in mitral stenosis,[16] pulmonary hypertension is reversible by surgery to a surprisingly large degree.[8] As a consequence of this, the intensity of very loud second pulmonic sounds frequently diminishes, the functional murmurs of pulmonic dilatation tend to disappear, the radiologic signs of pulmonary congestion and pulmonary-artery dilatation may decrease, and electrocardiographic signs of right-axis deviation and clockwise rotation usually lessen when these have been pronounced before surgery. Such diagnostic criteria as these are most likely to be present preoperatively in patients with severe pulmonary hypertension, and in those with pure stenosis and a minimum of factors known to have an adverse effect on the results.[17] It is in this "ideal" group that the clinical findings associated with altered hemodynamics most often change in the direction of normal and in which marked functional improvement is most consistent.

Certain postoperative radiologic findings have been disturbing to some investigators. An over-all increase in cardiac size is commonly noted on x-ray study in the immediate postoperative period, and was found by Soloff and Zatuchni[18] to be present in 11 of 20 patients six months after surgery. Although we seldom found increases in cardiac diameters measured on teleroentgenograms, a third of the patients in the present series had cardiac chambers or pulmonary vessels that were more abnormal in appearance after than before operation. We found that patients with radiologic evidence of deterioration were much less likely to have marked symptomatic improvement, and, as a group, they had three times as many "adverse factors" per patient than those demonstrating radiologic improvement. Furthermore, there were indications that such patients more often lose some of their initial symptomatic benefit during the first two postoperative years. Radiologic findings may prove to be important prognostic adjuncts to the postoperative management of patients. We have no evidence that rheumatic carditis plays a significant part in postoperative cardiac enlargement, as proposed by others.[18,19]

The electrocardiographic findings appear to provide considerable prognostic aid in the minority of cases in which signs of hypertrophy of the right ventricle are present. Such findings are correlated with the degree of pulmonary hypertension,[8,20] and with the total pulmonary resistance, which is a function of both pulmonary arteriolar resistance and mitral-valve area.[21] Such patients are also not likely to have mitral incompetence or any other disorder causing a strain on the left ventricle. Clinical improvement is generally accompanied by reversion toward normal of right-axis deviation, clockwise rotation and ST-segment and T-wave changes over the right ventricle. Incomplete right-bundle-branch-block patterns are not of prognostic importance, probably because they are not well correlated with elevated pulmonary-artery pressures.[20,22,23] In the patients who had electrocardiograms taken at intervals during the follow-up period, it is apparent that the reversion of preponderance of the right ventricle often occurs gradually over a period of many months. This is in accord with the observation that pulmonary vascular resistance, when very high, may show a gradual fall over a period of a year or more.[8]

Other electrocardiographic signs indicate less dramatic changes. The classic "P pulmonale," in contrast to certain cases of congenital heart disease with left-to-right shunt, is unusual in mitral stenosis.[22] However, prominent P waves often become smaller as the pulmonary hypertension and presumably dilatation of the right atrium diminish. The common mitral P wave, the form of which is believed to originate in the left atrium, does not change significantly. Cardiac rhythm also shows no important changes. Although many patients with normal rhythm may have fibrillation during the first postoperative week, this seems of no prognostic importance and of no danger in the presence of routine digitalization. Such paroxysmal arrhythmias, if persistent, can usually be converted with quinidine. Long-established atrial fibrillation, on the other hand, seems to be no easier to convert after surgery than before.

Only 8 of our patients had electrocardiographic signs of hypertrophy of the left ventricle in the follow-up period, and there was some reason for the enlargement in 6 of these. Only 1 of the 8 received marked symptomatic benefit, so that this finding probably has prognostic importance. When some degree of hypertrophy exists before surgery, a postoperative increase in the electric effect of the left ventricle may represent a diminished right-ventricle component. Never-

theless, some cases of progressive enlargement of the left ventricle can be expected to occur after operation, whether as a result of mitral incompetence, aortic-valve disease, unassociated vascular disease or rheumatic carditis. Serial electrocardiograms can be expected to provide important clues to such changes in ventricular size.

In addition to the objective findings that can be ascribed to diminished pressures proximal to the mitral valve, some changes can be ascribed to the altered valve structure alone. Thus, the tendency for the diastolic murmurs to diminish in intensity can be related to the wider aperture provided for passage of blood, and the fact that the change in this murmur more often occurs in the most improved group indicates that the production of mitral incompetence is not usually responsible for the dampening effect. The first heart sound shows a similar tendency to diminish, which, except as the result of the surgical production of mitral insufficiency, is correlated with clinical improvement.[8]

The fate of soft apical systolic murmurs is quite unpredictable, since some diminish or disappear after valvuloplasty whereas others make their appearance only in the postoperative period. There is, however, a distinct over-all tendency for apical systolic murmurs to be more numerous after surgery than before, a fact that has been noted by others.[9,18,24] Some can be explained by the surgical production of mitral regurgitation, especially if the murmur is very loud.[8] However, the majority of such new murmurs are soft, and there is a poor correlation between their appearance and the estimate of mitral incompetence after fracture of the valve. Such factors as altered valve structure and mobility, increased filling of the left ventricle and changes in velocity and turbulence of blood flow may also influence murmurs. Furthermore, in the absence of known mitral regurgitation, the intensification or appearance of soft apical systolic murmurs is of no prognostic value.

It is recognized that many patients with tight mitral stenosis have a low systolic pressure and small pulse pressure, although it is equally true that the blood pressure is of no importance in the diagnosis of mitral-valve disease.[25] Nevertheless, some patients appear to have a significant rise in systolic and pulse pressures after valvuloplasty that is presumed to be a manifestation of increased cardiac output. Wood[8] has recorded the small, rounded pulse characteristic of mitral stenosis by means of brachial-artery tracings, and has contrasted this with the "small water-hammer pulse" of mitral incompetence.

Although weight gain after mitral-valve surgery has not been reported previously, it was striking in some patients of the present series. This was true weight and did not represent edema. The gain occurred gradually over a period of a year or two. Whether this was due to physiologic or psychologic factors is a matter for speculation, but it seems to be correlated with the degree of functional improvement. Occasionally, frank obesity may appear, requiring caloric restriction.

Summary

One hundred and six patients with operatively treated mitral stenosis were followed for one to four and a half years. Certain objective clinical findings in these patients before and after mitral valvuloplasty are described and discussed. Changes that could be chiefly ascribed to alteration of the valve structure were the reductions in intensity of the mitral diastolic murmur and first heart sound in about half the patients. The frequent production of a soft apical systolic murmur after valvuloplasty was not related to the surgeon's estimate of mitral incompetence after valve fracture, and seemed to have no prognostic importance. The absence of an apical systolic murmur before surgery was good evidence that serious or prognostically significant mitral regurgitation did not exist.

Changes related to the reduction of pressures proximal to the mitral valve included the diminution in intensity of a loud second pulmonic sound in a third of the patients, the frequent disappearance of functional murmurs of pulmonary dilatation, definite radiologic improvement in 41 per cent of 54 patients and reversion toward normal of electrocardiographic signs of right-axis deviation and clockwise rotation whenever these were pronounced before surgery. Most of these changes were roughly correlated with the degree of symptomatic improvement.

Certain objective signs showed postoperative deterioration in a significant number of patients: a change for the worse in 31 per cent of 54 x-ray studies, and postoperative electrocardiographic evidence of hypertrophy of the left ventricle in 8 per cent of the series. Such changes occurred more often in a prognostically unfavorable group, but we were unable to implicate rheumatic fever as a cause of poor results or deterioration during the follow-up period.

The presence of palpable valvular calcium could be predicted in almost all cases by preoperative fluoroscopy, a finding of some prognostic significance since mitral insufficiency was much more frequent in calcified valves. However, the radiologic diagnosis of mitral regurgitation by determination of atrial systolic expansion was, in our experience, of no value when the incompetence was not predominant.

An excellent clinical result could be anticipated in most of the patients with electrocardiographic signs of hypertrophy of the right ventricle, since these signs are probably a measure of marked pulmonary hypertension amenable to surgical relief. The presence of patterns of incomplete right-bundle-branch block alone had no prognostic significance. In some cases significant increases in systolic and pulse pressures followed valvuloplasty. Greatly improved patients often showed striking increases in body-tissue weight.

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ABSORPTION OF RADIOACTIVE VITAMIN B_{12} IN NONANEMIC PATIENTS WITH COMBINED-SYSTEM DISEASE*

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BEFORE the advent of liver or vitamin B_{12} treatment of pernicious anemia, approximately 80 per cent of patients who died of this disease had neurologic signs resulting from demyelinization of the posterior and lateral columns of the spinal cord.[1] This neurologic disorder has been variously termed combined-system disease, posterolateral sclerosis, subacute combined degeneration of the spinal cord and funicular degeneration. Its pathology, clinical course and response to treatment are well known.[2-7]

In vitamin B_{12} deficiency, anemia usually precedes the development of neurologic signs and symptoms, but occasionally this sequence is reversed and extensive neurologic damage may occur in the absence of marked hematologic changes.[8-24] Because the signs and symptoms of combined-system disease are produced by altered functions of specific nerve tracts, similar anatomic lesions of whatever origin produce similar clinical manifestations, which are therefore not peculiar to vitamin B_{12} deficiency. The recent development of methods of measuring the gastrointestinal absorption of radioactive vitamin B_{12} presents a presumptive means of differentiating combined-system disease resulting from vitamin B_{12} deficiency from similar neurologic disorders not related to such a deficiency.

Many cases of combined-system disease have been described in nonanemic patients, but in almost all, pathological confirmation of this diagnosis is lacking.[8-24] Combined-system disease has also been reported in association with a wide variety of other diseases. However, autopsy examination is not available, and hematologic data are insufficient to exclude the presence of pernicious anemia in these reports.[19]

Suh and Merritt[8] presented 8 cases of combined-system disease without pernicious anemia in 1938. They considered the disorder identical to that encountered in association with pernicious anemia and believed that it is due to the same etiologic factors. We have reviewed the course of events in these patients since then. Despite intensive treatment with liver extract, 2 patients died with progressive neurologic disease later considered to be "atypical multiple sclerosis." A third patient was re-examined after seven years without liver-extract or vitamin B_{12} treatment, and the diagnosis of peripheral neuritis was made. Autopsy findings in a fourth patient, reported in the original article, consisted of "slight degree of demyelinization in the posterior columns . . . in the crossed pyramidal tracts . . . and diffusely

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scattered throughout the brain." A fifth patient, who made no improvement and who possibly had an increase in neurologic signs despite treatment with liver extract, died of carcinoma of the rectum ten months later. One patient was known to have had congenital syphilis, and another had Hodgkin's disease at the time of the original report. One patient is still alive and has had moderately progressive spinal-cord involvement despite intensive liver-extract therapy.

dinarily present in food. In pernicious anemia, the absence of intrinsic factor results in a deficiency of the vitamin that leads to the hematologic and neurologic manifestations of the disease. Only 5 reports have been found in the literature regarding the presence or absence of intrinsic factor in nonanemic patients suspected of having combined-system disease. In each of these studies, gastric juice from the patients was incubated with beef muscle and then administered orally to patients with pernicious

TABLE 1. *Clinical and Laboratory Data on Nonanemic Patients with Combined-System Disease.*

Patient	Sex	Age	Chief Symptom	Duration of Symptom before Treatment	Tongue Papillae	Gastric Acidity after Histamine	Neurologic Signs before Treatment: Deep Tendon Reflexes*	Plantar Responses	Vibration Sense	Position Sense	Other Neurologic Signs	Lumbar Puncture, Blood & Cerebrospinal-Fluid Wassermann Test & Skull X-Ray Examination
		yr.		mo.								
W.R.	M	78	Numbness of feet	17	Markedly decreased	Absent	+++ ankle & knee jerks	Bilateral flexor	Absent distal to wrists & knees	Absent distal to wrists & knees	None	Negative
W.T.	M	61	Numbness of hands & feet	6	Markedly decreased	Absent	++++ ankle & +++++ knee jerks	Bilateral extensor	Absent distal to wrists & knees	Absent distal to wrists & knees	Spastic gait	Negative
P.B.	F	66	Numbness of hands & feet	9	Absent	Absent	++++ ankle & knee jerks	Bilateral flexor	Absent distal to knees & right wrist	Absent distal to knees & right wrist; decreased left wrist	None	Negative
A.L.	M	66	Unsteady "numb" legs	18	Moderately decreased	Absent	+++ ankle & knee jerks	Flexor on right; equivocal on left.	Absent distal to wrists & knees	Absent in toes; decreased in all fingers.	"Stocking" type of hypesthesia in feet; moderately spastic gait.	Negative

*In evaluating deep tendon reflexes:
2 + normal activity
3 + moderately hyperactive
4 + markedly hyperactive
5 + markedly hyperactive with unsustained clonus
(reflexes were normal unless otherwise stated)

It therefore appears that although these patients had signs and symptoms of combined-system disease when they were first observed, the course of events suggests that vitamin B_{12} deficiency was not related to the neurologic disease. Since at that time technics for measuring intrinsic-factor activity were involved and laborious, clinical evaluation of response to treatment was the best available means of ascertaining the etiology of the neurologic disorder in these patients. However, treatment included not only liver extract but also the associated physiotherapy, rest and reassurance. If normal intrinsic-factor activity had been demonstrated, the diagnosis of combined-system disease due to the same mechanism found in pernicious anemia would not have been tenable.

Intrinsic-factor activity is essential for adequate absorption of the small amounts of vitamin B_{12} or-

anemia in relapse. Castle, Heath and Strauss,[20] Reimann and Weil[21] and Briggs and Oerting[22] demonstrated significant reticulocyte responses in the recipients. This was interpreted as indicating the presence of intrinsic factor in the gastric juice used. Beebe and Wintrobe[23] and Palmer and Porter,[24] using gastric juice from similar donors, failed to demonstrate reticulocyte responses in similar recipients and concluded that the gastric juice from the nonanemic patients with neurologic disease was deficient in intrinsic-factor activity. Studies of this type were impeded by the decreasing number of suitable patients with untreated pernicious anemia, as well as by the difficulties of such an assay.

Clarification of the problems of diagnosis has been made possible by the biosynthesis of cobalt^{60}-labeled vitamin B_{12} of relatively high specific activity. Ab-

sorption of the radioactive vitamin from the gastrointestinal tract may be determined by measure of its fecal elimination (Heinle and Welch[25]), urinary excretion (Schilling[26]) or hepatic deposition (Glass et al.[27]). Pollycove and Apt[28] have compared these methods and have shown that they yield results of comparable accuracy.

In this study the hepatic deposition of cobalt^{60}-labeled vitamin B_{12} was employed to assay the intrinsic-factor activity in nonanemic patients whose red-cell macrocytosis, occasional giant metamyelocytes and band forms in the aspirated bone marrow, but no reduction in hemoglobin. After treatment with vitamin B_{12}, he experienced marked objective and subjective neurologic improvement over a six-month period. He died of a cerebral hemorrhage four years later. The fourth patient had gastric achlorhydria but no anemia at the time the diagnosis was made; he was not seen again before he died. Autopsy was not performed in any of these 4 patients.

TABLE 1 *(Concluded).*

	Hematologic Findings before Treatment										
Patient	Hemoglobin	Hematocrit	Red-cell count	White-cell count	Peripheral-blood morphology	Bone-marrow morphology	Duration of treatment at time of evaluation	Neurologic response to vitamin B_{12} treatment	Hematologic response to vitamin B_{12} treatment	Other diseases present	Interval between 1st symptoms & Cobalt^{60}-labeled vitamin B_{12} studies
	gm./100 cc.	%	*x 10⁶*	*x 10³*			*mo.*				*mo.*
W.R.	14.0	—	—	7.5	Normal	——	5	Subjective decrease in paresthesias; slight return of position sense in hands.	None	Arteriosclerotic heart disease, mild	18
W.T.	14.0	41	4.0	7.0	Rare, round macrocyte	Rare macronormoblast & giant band forms	22	Marked subjective improvement; return of all vibration & position senses.	Disappearance of peripheral blood & bone-marrow changes, without reticulocytosis or rise in hemoglobin	Psoriasis, generalized	22
P.B.	13.5	42	—	8.0	Normal	——	96	Moderate return of vibration & position senses in hands	None	Inactive pulmonary tuberculosis	96
A.L.	13.5	40	3.9	9.0	Rare, round macrocyte	Occasional macronormoblast	2	Markedly decreased spasticity; moderate return of vibration & position senses.	Disappearance of peripheral blood & bone-marrow changes, with 5% reticulocytosis on 6th day without rise in hemoglobin	None	18

illnesses had been diagnosed as combined-system disease.

Clinical Material

The data in the present study were obtained from the records of 9 patients who had been hospitalized at the West Roxbury, Cushing or Boston Veterans Administration hospital during the period 1944-1954 and from personal observation of 4 of these patients.

All 9 patients suffered from illnesses diagnosed as combined-system disease. None had evidence of major hematologic disorders at the time the diagnosis was made. There was no history of previous treatment with vitamin B_{12}, liver extract or folic acid.

Four of these patients were dead at the time this study was undertaken. The progression of disease described in 1 patient suggested multiple sclerosis. Progressive paraplegia occurred in a second patient despite frequent liver-extract injections. A third patient had no free hydrochloric acid in his gastric juice after histamine stimulation, minimal peripheral

A fifth patient who had changes similar to the third patient, and a similar response to treatment, was not available for further study.

Three of the remaining 4 patients (W.R., W.T. and P.B.) had been receiving vitamin B_{12} treatment for five to ninety-six months before determination of intrinsic-factor activity by means of radioactive vitamin B_{12}. The fourth patient (A.L.) was studied before and after vitamin B_{12} treatment. His serum vitamin B_{12} concentration was 32 micromicrogm. per cubic centimeter before treatment (within the range associated with pernicious anemia in relapse[29]). In all 4 patients treatment produced subjective and objective neurologic improvement. Clinical and laboratory data pertaining to these 4 patients before and after vitamin B_{12} treatment are presented in Table 1.

A group of 11 patients ranging in age from sixty-seven to eighty-six served as controls for similar radioactive studies. These patients had neither signs nor symptoms of disease of the posterior and lateral columns, were not anemic, had never been treated for anemia and had not had any gastric surgery.

Methods

The hepatic deposition of cobalt^{60}-labeled radioactive vitamin B_{12} after oral administration, with and without normal human gastric juice, and after subcutaneous administration was measured by the technic of Glass et al.[27] In all cases the same lot of crystalline cobalt^{60}-labeled vitamin B_{12} with specific activity of 0.786 microcuries per microgram was used in the preparation of the test doses of 0.5 microgm. each. External monitoring was performed with a scintillation counter placed on the subject's skin overlying the middle zone of hepatic dullness in the midaxillary line. The left lower thigh was similarly monitored to determine the background counting rate. The counting rate of the operator's body and the counting rate in air were also ascertained. External monitoring was performed before and ten days after the test material was given. After subcutaneous injections the site was monitored to demonstrate complete absorption. Hepatic counts per minute per microcurie were determined ten days after oral administration alone, ten days after subcutaneous administration and ten days after the administration of an oral test dose with human gastric juice. All counts were corrected for the physical decay of cobalt^{60}.

Table 2. *Hepatic Deposition of Cobalt^{60}-Labeled Vitamin B_{12} in Nonanemic Patients with Combined-System Disease.*

Subject	Hepatic Count after Injection of Radioactive Vitamin	Hepatic Count after Oral Ingestion of Radioactive Vitamin	Deposition in Liver after Oral Test Dose	Hepatic Count after Oral Ingestion of Radioactive Vitamin + Normal Gastric Juice	Deposition in Liver after Oral Test Dose + Normal Gastric Juice
	per min./ microcurie	*per min./ microcurie*	*%*	*per min./ microcurie*	*%*
P.B.	5116	171	3		
W.R.	6682	1281	19	3383	51
W.T.	5356	0	0	3336	62
A.L.:					
Before treatment	6351	569	9	1746	28
After treatment	7065	418	6	3495	50

The percentage of absorption after oral administration was calculated by division of the subsequent hepatic count per minute per microcurie by that observed after *subcutaneous* administration and multiplication by 100. The hepatic count after *subcutaneous* administration was assumed to represent "100 per cent absorption."

Serum vitamin B_{12} analysis was kindly performed by Dr. Arnold A. Lear, of the Thorndike Memorial Laboratory, Boston City Hospital, using the *Euglena gracilis* microbiologic assay method of Ross.[30]

Gastric juice was collected with gentle suction after histamine stimulation; 80 to 150 cc. was collected in each case. This was immediately filtered through a coarse-glass filter, and the pH adjusted to 7.3-7.7 with 10 per cent sodium hydroxide, bromphenol blue being used as an indicator. When not analyzed immediately the juice was frozen and stored at −10°C.

Results

The hepatic deposition of radioactive material in the nonanemic patients with combined-system disease is presented in Table 2. After an oral test dose the hepatic count per minute per microcurie varied from 0 to 19 per cent of the values that followed subcutaneous injection of a similar dose. When the same oral dose was administered together with normal human gastric juice, the hepatic count varied from 59 to 63 per cent of the values obtained after injection.

Patient A.L., before treatment with vitamin B_{12}, had 27 per cent hepatic deposition of an oral labeled dose given on two separate occasions with 150 cc. of normal human gastric juice that was shown to possess intrinsic-factor activity when tested in patients with treated pernicious anemia. After treatment with vitamin B_{12}, the deposition of the oral test dose administered together with normal gastric juice was 49 per cent on each of two occasions.

Gastric juice collected from each of the 4 nonanemic patients with combined-system disease was given orally with a test dose of radioactive vitamin to each of 4 patients with treated pernicious anemia. At ten-day intervals each of these 4 patients was also given the test dose orally without gastric juice, an identical subcutaneous dose, and a similar oral test dose with 150 cc. of normal human gastric juice. The results of these tests are presented in Table 3.

Table 3. *Hepatic Deposition of Cobalt^{60}-Labeled Vitamin B_{12} in Patients with Pernicious Anemia Who Received Gastric Juice from Nonanemic Patients with Combined-System Disease.*

Subject with Pernicious Anemia	Hepatic Count after Injection of Radioactive Vitamin	Hepatic Count after Oral Ingestion of Radioactive Vitamin		Hepatic Count after Oral Ingestion of Radioactive Vitamin + Gastric Juice from Patients with Combined-System Disease		Hepatic Count after Oral Ingestion of Radioactive Vitamin + Normal Gastric Juice	
	per min./ microcurie	*per min./ microcurie*	*%*	*per min./ microcurie*	*%*	*per min./ microcurie*	*%*
I.N.	4411	0	0	0 (W.T.)	0	3440	78
G.A.	4633	286	6	0 (A.L.)	0	2716	59
J.C.	5779	148	3	481 (W.R.)	8	3587	62
W.K.	6088	0	0	162 (P.B.)	3	3398	57

The hepatic deposition of orally administered vitamin B_{12} in these treated patients was 0 to 6 per cent of that after subcutaneous administration of the test dose. After ingestion of the same test dose with normal human gastric juice, the comparable hepatic deposition ranged from 59 to 78 per cent.

When gastric juice collected from each of the nonanemic patients with combined-system disease was given with the test dose of radioactive vitamin to the patients with treated pernicious anemia, the hepatic deposition ranged from 0 to 8 per cent of that observed after the subcutaneous test done.

The hepatic deposition of cobalt^{60}-labeled vitamin B_{12} ten days after both oral and subcutaneous administration to the control patients is shown in Table 4. The average hepatic deposition of an oral test dose ranged from 40 to 68 per cent of the subcutaneous value. Five of these patients had histamine-fast achlorhydria; 5 exhibited free hydrochloric acid (1 was not examined for this).

Discussion

The average hepatic deposition of an oral test dose of 0.5 microgm. of cobalt^{60}-labeled vitamin B_{12} in the control group was significantly less than that obtained when healthy young men were similarly studied.[28] The lowest hepatic deposition of the oral test dose in the control group was 40 per cent. No doubt, examination of a large group of subjects in this age group would reveal an occasional patient who would have no intrinsic-factor activity but neither hematologic nor neurologic manifestations of vitamin B_{12} deficiency. This statement is based on the demonstration of complete absence of intrinsic-factor activity after total gastrectomy by Halsted, Gasster and Drenick[31] and by the data of MacDonald and his associates[32] indicating that four or five years are usually required for pernicious anemia to develop after total gastrectomy when no vitamin B_{12} has been given parenterally and no folic acid by mouth. It is therefore to be expected that, in rare cases, patients with disease of the posterior and lateral columns that is *not* produced by vitamin B_{12} deficiency may have deficient intrinsic-factor activity unrelated to their neurologic disease. In these exceptional patients, failure to respond to vitamin B_{12} treatment and progressive neurologic disease despite such treatment may be the only indication that the disease of the posterior and lateral columns was not due to vitamin B_{12} deficiency.

In this study both the treated patients with pernicious anemia and the nonanemic patients with combined-system disease had less than 19 per cent hepatic deposition of the oral radioactive test dose; in 7 of 8 patients the deposition was less than 9 per cent. The difference in hepatic deposition between these two groups and the control group is striking and presumably represents virtually complete absence of intrinsic-factor activity in the first two groups. Further demonstration of the lack of intrinsic-factor activity in the nonanemic patients with combined-system disease was obtained when their gastric juice failed to increase the hepatic deposition of an oral test dose given to the patients with treated pernicious anemia. The patients in both these groups demonstrated significant increases in hepatic deposition of the oral test dose given with normal human gastric juice.

In the absence of autopsy data in these 4 cases, one cannot completely exclude the possibility that there was no relation between the demonstration of absent intrinsic factor and the neurologic disease. This is most unlikely in patient A.L., who was shown to have had a serum vitamin B_{12} concentration before treatment that was within the range associated with pernicious anemia in relapse.[29] Minimal hematologic morphologic signs of vitamin B_{12} deficiency were present in 2 patients and disappeared after treatment. Each patient had some objective neurologic improvement after vitamin B_{12} treatment; no adverse progression of neurologic signs was noted during the follow-up period, which ranged from two to ninety-six months.

Table 4. *Hepatic Deposition of Radioactive Vitamin in Control Group.*

Subject	Age	Gastric Acidity after Histamine Stimulation	Hepatic Count after Injection of Radioactive Vitamin	Hepatic Count after Oral Ingestion of Radioactive Vitamin	
	yr.		*per min./ microcurie*	*per min./ microcurie*	*%*
H.A.	87	Absent	7640	4112	54
P.B.	75	Present	4963	1972	40
D.C.	67	Absent	6620	3227	49
S.H.	70	Present	6640	3525	53
W.K.	73	Absent	6813	3209	47
H.M.	68	———	6958	3357	48
J.M.	72	Absent	6399	3938	62
E.R.	68	Present	7901	3702	47
F.R.	67	Present	4563	2326	51
S.S.	73	Present	5861	4012	69
S.T.	72	Absent	5660	3100	55

Vitamin B_{12} deficiency resulting from deficient intrinsic-factor activity becomes more frequent with age; the majority of patients are over fifty years of age at the time the diagnosis is first made.[33] The rate of occurrence of histamine-fast achlorhydria in otherwise normal patients who are fifty years old is estimated to be 20 per cent.[34] Hence, the finding of achlorhydria in nonanemic patients of this age group who are suspected of having combined-system disease due to vitamin B_{12} deficiency does not necessarily indicate deficient intrinsic-factor activity. Five of the control patients had histamine-fast achlorhydria with no evident relation to the degree of intrinsic-factor activity (Table 4).

Normal gastric acidity and intrinsic-factor activity have been associated with vitamin B_{12} deficiency in a small group of patients who have either dietary deficiency of vitamin B_{12} or difficulty in absorbing the vitamin from the gastrointestinal tract because of fish-tapeworm infestation, sprue or other abnormal-

ities of the small intestine.[35-38] In all these conditions signs of vitamin B_{12} deficiency in the nervous system have been strikingly minimal.

This study has not provided any indication why some patients with intrinsic-factor deficiency have neurologic manifestations of vitamin B_{12} deficiency with normal hematologic findings. Because there are no methods for determining folic acid concentrations in tissue, the concept that adequate folic acid absorption from the gastrointestinal tract permits the development of neurologic disease but not the hematologic manifestations of vitamin B_{12} deficiency remains conjectural.[39]

Summary and Conclusions

Four nonanemic patients with combined-system disease were found to lack intrinsic-factor activity, leading to the assumption that the neurologic disorder was due to vitamin B_{12} deficiency. None of these patients had received folic acid supplements.

Clinical states mimicking combined-system disease can occur as a result of involvement of the posterior and lateral columns of the spinal cord by pathologic processes of varied etiology. When the characteristic hematologic abnormalities of pernicious anemia are absent, the measurement of intrinsic-factor activity by the hepatic deposition of radioactive vitamin B_{12} may serve to differentiate combined-system disease due to vitamin B_{12} deficiency from this other group of diseases.

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ACUTE HEMOLYTIC ANEMIA, CRYOGLOBULINEMIA AND COLD AGGLUTINATION*

Report of a Case

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THE term cryoglobulinemia, from the Greek κρύος meaning cold, was coined by Lerner and Watson[1] to describe abnormal globulins that have the physical characteristics of precipitating on cooling and redissolving on subsequent warming. These authors reviewed the fourteen prior reports on this subject.[2] In addition to cases associated with subacute bacterial endocarditis[3] and other diseases that occasionally exhibit small amounts of cryoglobulins,[2,4] 20 cases of high-grade cryoglobulinemia have since been reported.

Rørvik[5] has recently described a patient with severe Raynaud syndrome who had an extremely high cold-agglutinin titer and cryoglobulinemia, and a mild chronic hemolytic anemia. Previously, Craig et al.[6] had reported the case of a patient with both acute hemolytic anemia and cryoglobulinemia. The purpose of this communication is to present and discuss a case of acute hemolytic anemia associated with cryoglobulinemia and cold hemagglutination.

CASE REPORT

On March 27, 1953, J.P. (N.H.H. 38-57-38), an 81-year-old widow, was admitted to the General Medical Service of the Grace–New Haven Community Hospital on the private service of Dr. Vincent Grillo. She complained of pain in the lower back and jaw, weakness, fatigue and anorexia.

The patient had generally enjoyed fair health. Eight years before, she had had a cerebrovascular accident but had subsequently regained speech and motor function completely. A number of years previously she was found to have diabetes mellitus, treated with a liberal diet and small doses of NPH insulin. There was no history of either diabetic acidosis or hypoglycemic episodes.

A review of the systems was negative.

One month before admission chest pain, dyspnea and persistent aching of the lower back developed, progressively increasing in severity. There were moderate hypertension, rales at both lung bases and ankle edema. Treatment with digitalis and sublingual nitroglycerin was effective.

Progressive weakness ensued. Four days before admission the urine darkened. No observations of the stool color had been made. The patient, although anorectic, did not have nausea, vomiting or abdominal pain. No jaundice or pruritus was noted, but at the time of admission she was found to be deeply icteric.

Physical examination, which showed an acutely ill woman who, although stuporous, could be roused, was negative except for the findings mentioned below. The skin was deeply jaundiced, with poor turgor. No purpura, petechiae or arterial angiomas were noted. The fundi showed moderate arterial tortuosity and attenuation, but no exudates or hemorrhages. No lymph nodes of significant size were palpable. There was decreased resonance posteriorly at the right base, with coarse rales heard at both lung bases, more marked on the right. The point of maximal impulse and left border of cardiac dullness were in the anterior axillary line. Normal sinus rhythm was present. A Grade 2 apical systolic murmur could be heard along the left sternal border. The abdomen was protuberant and tympanitic, but no ascitic fluid could be demonstrated. A firm, sharp, nontender liver edge was easily palpable 5 fingerbreadths below the right costal margin in the midclavicular line. The spleen, palpable 3 fingerbreadths below the left costal margin, was firm but not tender. Strong arterial pulsations were present in all extremities. There was no cyanosis, edema, venous distention or scarring. Neurologic examination was negative.

The temperature was 100.2°F., the pulse 88, and the respirations 24. The blood pressure was 142/90.

On the day after admission the red-cell count was 1,180,000, with a hemoglobin of 4.7 gm. per 100 cc., a hematocrit of 24 per cent and reticulocytes of 15 per cent; the corrected sedimentation rate was 65 mm. per hour (Wintrobe method). The white-cell count was 10,000, with 83 per cent neutrophils, 9 per cent lymphocytes and 8 per cent monocytes. The peripheral blood showed marked rouleaux formation and microcytic, hypochromic and anisocytic cells as well as spherocytes. Examination of the bone marrow disclosed tremendous erythroid hyperplasia overshadowing the myeloid series, which appeared normal. The bilirubin was 0.41 mg. and 2.56 mg. per 100 cc. at 1 and 30 minutes respectively. It was impossible to type the blood at room temperature, because of the marked autoagglutination. An attempt to do so on a warmed slide similarly failed.

Dr. T. S. Evans suggested that the acute hemolytic episode was due to the cold agglutination. In the presence of a severe anemia of unknown cause and in the face of hemagglutination that defied blood transfusion the patient received only supportive therapy.

On March 30 the Coombs test was found to be ++++ at room temperature but negative at 37°C. Cold agglutinins were ++++ in a dilution of 1:1024 (dilution not carried farther), but at 37°C. there was no agglutination. The bilirubin at 1 minute and 30 minutes was 0.38 and 2.00 mg. per 100 cc. respectively. Bromsulfalein retention at 45 minutes was 13.4 per cent; cephalin-flocculation was ±, and the alkaline phosphatase was 11.2 Bodansky units. The urine was negative for bile and hemoglobin. Red-cell fragility was normal.

The patient had not improved since admission. On the 4th hospital day, cortisone therapy was started, with an initial dose of 300 mg. followed by 200 mg. each day in divided doses. The cold-agglutinin titer at this time was 1:1,048,576. No in vivo hemolysis was noted.

During the following 10 days the patient dramatically improved both clinically and by laboratory determinations. The jaundice faded; she became alert and regained her appetite and strength. Fine inspiratory rales could still be heard at both bases. The hemoglobin rose to 7.5 gm. per 100 cc., and the red-cell count to 1,510,000. Cortisone was gradually discontinued after 14 days of therapy.

On April 15 cryoglobulins were discovered, and special studies were carried out. The 1-minute bilirubin had fallen to 0.20 mg., and the 30-minute to 1.80 mg. per 100 cc. The liver-function tests had all reverted to normal. The nonprotein nitrogen, previously 69 mg., was 43 mg. per 100 cc. An electrocardiogram showed a left-bundle-branch block. A tourniquet test gave no evidence of abnormal capillary fragility. Until the time of discharge, the patient continued to improve. The hemoglobin had reached 9.5 gm. per 100 cc., and the red-cell count about 2,000,000, and the urine was normal except for a trace of albumin.

She was well at home until late July, when, after an acute respiratory infection severe jaundice accompanied by left-upper-quadrant pain, presumably caused by a recurrent

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hemolytic episode, again developed. She refused admission to the hospital at that time and died at home. No laboratory studies were performed, and permission for post-mortem examination was not obtained.

Special Studies

On April 15 serum that had been kept in a refrigerator at 5°C. for several hours was found to have a small translucent button at the bottom of the test tube. This button dissolved on warming. As the temperature was lowered to 10°C. a moderately heavy flocculant precipitate appeared, settled and formed a gel in the test-tube butt. Repeated heatings and coolings did not alter these characteristics.

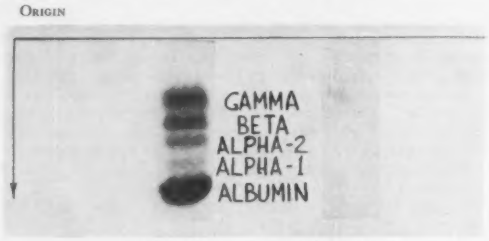

FIGURE 1. *Filter-Paper Electrophoresis of Cryoglobulin. The control pattern is that of a normal patient. The cryoglobulin migrated with the mobility of gamma globulin, as evidenced by the protein seen only in the gamma-globulin zone.*

This specimen of serum was examined for total protein, albumin and globulin by the Kjeldahl technic, 26.88 per cent sodium sulfite being used to precipitate globulin. The total protein was 5.72 gm., the albumin 3.45 gm., and the globulin 2.27 gm. per 100 cc. Filter-paper electrophoresis of this specimen by the technic previously described from this laboratory[7] showed the albumin to be decreased but the globulin components to be normal.

On April 21 blood was drawn, allowed to clot and centrifuged at 37°C. in the hope of demonstrating a greater amount of cold-precipitable globulin, as reported by Barr et al.[8] No additional cryoglobulin was found by chemical determination. Similar specimens of serum were examined simultaneously by filter-paper electrophoresis before and after the cryoglobulins had been precipitated. There were no significant differences between these specimens.

The cryoglobulin was separated by cold precipitation, centrifugation and repeated washings with physiologic saline solution at 5°C. Analysis of this material by the micro-Kjeldahl technic showed that the serum contained 170 mg. of cryoglobulin per 100 cc.

This cryoglobulin was almost entirely soluble in barbitone electrophoretic buffer (pH 8.60 and ionic strength 0.05). A specimen was examined with the technic of filter-paper electrophoresis of Grassmann and Hannig[9] modified to permit examination at a temperature of 37°C. Twenty microns of this solution were applied to Whatman No. 1 filter paper by a micropipette in the manner previously described.[7] Simultaneously, a normal serum was examined to serve as a control. The cryoglobulin migrated with the mobility of a gamma globulin (Fig. 1).

Discussion

In the decade since cryoglobulins were first named and defined a large number of additional cases of cryoglobulinemia have been reported. These cases fall into several broad clinical classifications. In kala-azar, which often exhibits abundant amounts of cryoglobulin,[4] and in subacute bacterial endocarditis, in which minute amounts are frequently found,[3] the primary clinical pictures are fairly well defined. Almost two thirds of all the other patients suffered from cold sensitivity varying from simple urticaria with subsequent purpura[10] to the full-blown Raynaud syndrome[11,12] and even to subsequent necrosis and ulceration.[13] Approximately half the patients had epistaxis, purpura or other evidences of altered blood coagulation. Except for the common bond of cryoglobulinemia the rest of the cases bear little clinical similarity to each other.

The diagnosis of multiple myeloma has been established in approximately half the reported cases, and chronic lymphatic leukemia accounts for about a fifth. A still smaller percentage falls into an intermediate zone based on the histologic appearance of the abnormal cells. No definite diagnosis was established in the remainder of these cases.

The case described above differs considerably from the more common clinical picture seen in cryoglobulinemia. This patient did not exhibit cold sensitivity, Raynaud's phenomenon, epistaxis, purpura or other bleeding tendencies. The primary problem was that of an acute hemolytic anemia. The case was further remarkable in that a cold-agglutinin titer greater than 1:1,000,000 was found; this is one of the highest titers recorded.[14]

The cold-agglutinin titer was significantly elevated in only 2 previously recorded cases of cryoglobulinemia.[5,11] In 1 of these[11] it was shown that the cold-hemagglutinin titer of 1:1024 was resident in the cryoglobulin itself. In the other[5] the titer reached the enormous level of 1:168,000,000, the highest recorded in the literature. This patient suffered from acrocyanosis and Raynaud's syndrome on exposure to cold. In addition, she was shown to have a chronic hemolytic process of undetermined etiology. Rørvik believes that the cold agglutinins present behaved as cryoglobulins. No studies were performed to clarify this point.

The relation of cold agglutinins and cryoglobulins deserves further study. No cryoglobulins have been noted in any of the other cases with significant cold-agglutinin titers. On the other hand, Barr et al.[8] have shown that their cryoglobulin caused only a very low titer of pseudoagglutination — that is, the red cells appeared to be enmeshed in a precipitate. This phenomenon was also observed in the case reported above. Several other patients with cryoglobulinemia have had very low cold-agglutinin titers. It appears that in the case described above, these two phenomena were independently present.

Kala-azar is the only other condition in which both cryoglobulinemia[15] and a high cold-agglutinin titer[16] have been described, although not in the same patient. It is possible that in these cases the high titer was due to the presence of unrecognized cryoglobulins. However, the clinical course of kala-azar does not simulate that of any of the previously described cases of cryoglobulinemia nor that of the case presented above.

The only previous case reported in which cryo-

globulinemia and acute severe hemolytic anemia were associated[6] was in an elderly woman with chronic lymphatic leukemia who manifested a severe hemolytic process that responded dramatically to ACTH. Over a period of several years she was found to exhibit a high-grade cryoglobulinemia, which appeared at about the time of the onset of the autoimmune hemolytic disease. The authors apparently did not believe that the cryoglobulins were pathogenetically related to the hemolytic process.

High cold-agglutinin titers have been described most commonly in primary atypical pneumonia[17] but also in trypanosomiasis,[18] tropical eosinophilia[19] and occasionally in mumps orchitis[20] and infectious mononucleosis.[21] Rarely, the titer reaches very high levels without any apparent clinical cause. These titers have frequently been associated with acute hemolytic episodes and are believed to be responsible for some of the cases of hemolysis.[14,22,23]

Stats[24] has shown that potent cold agglutinins greatly increase the mechanical fragility of the red blood cells. The hypothesis of Castle and his coworkers[25] suggests the mechanism of in vivo agglutination, erythrostasis and local ischemia, followed by the liberation of substances that autolyze the red blood cells. Ham[26] caused intravascular hemolysis in a patient with a high cold-agglutinin titer by partial exposure to cold.

In the case reported above, the origin of the cold agglutinins is unknown. The patient had not received any sulfonamides. There was very little to suggest any of the diseases associated with cold hemagglutination. It is possible that the patient had primary atypical pneumonia, which may cause minimal clinical symptoms. Unfortunately, no chest roentgenogram had been obtained during the acute phase of the hospital course.

The nature of the underlying disease producing the cold-precipitable globulins in this case is also unknown. The bone-marrow examination did not remotely suggest a myelomatous or lymphomatous process. No definite diagnosis was established.

The relation between the cold agglutinins and the cryoglobulins and the hemolytic anemia is obscure. The theory of Dameshek and Miller[27] of injury to the erythrocytes by the agglutinins and subsequent hemolysis secondary to the trauma of circulation seems most likely. One may also speculate that two independent agglutinating influences, simultaneously active, might more easily and more critically damage the erythrocytic membrane than either substance alone.

In the final analysis one can only mention the concurrence of cryoglobulinemia, cold agglutinins and acute hemolytic anemia in this case.

Summary

A case of essential cryoglobulinemia associated with acute hemolytic anemia and a high titer of cold agglutination is presented.

The relation of cold agglutination and cryoglobulinemia to each other and to acute hemolytic anemia is discussed.

Evidence is presented that this particular cold-precipitable globulin had the mobility of a gamma globulin by filter-paper electrophoresis.

I am indebted to Dr. Theodore S. Evans, chief of the General Medical Service of the Grace–New Haven Community Hospital, who directed the clinical investigation and helped in the preparation of this manuscript.

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ACUTE VASCULAR (SCHÖNLEIN–HENOCH) PURPURA — AN IMMUNOLOGIC DISEASE?*

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THIS paper deals with a study of 15 cases of acute vascular (Schönlein–Henoch) purpura seen on the wards of the Boston Floating Hospital during 1948 to 1951. In 1950-51, when most of our cases were studied, there appeared to be a definite increase in the incidence of this condition in the Boston area. We became impressed with the generalized character of the disease, and with the possibility that it was related to the group of collagen diseases, which include such conditions as disseminated lupus erythematosus, periarteritis nodosa and possibly acute glomerulonephritis and serum sickness as well. Skin biopsies were performed in some cases in an attempt to determine whether or not changes similar to those found in the collagen disorders were present and to trace the natural history of this condition.

TABLE 1. *Pertinent Data in Cases of Acute Vascular Purpura.*

PATIENT	AGE	ANTECEDENT INFECTION	IMMEDIATE TREATMENT	TIME OF ONSET OF PURPURA	URTICARIA	JOINT PAINS	HEMATURIA
	yr.			*days*			
S.C.	4½	Sore throat	Penicillin	5	Present	Present, with swelling of left ankle & right elbow	Absent
J.M.	4½	Tonsillitis	Chlortetracycline	10	Present	Present	Absent
M.R.	4	Pharyngitis & tonsillitis	Penicillin & sulfonamide	21	Present	Present	Absent
A.G.	2½	Pharyngitis & tonsillitis	Penicillin by mouth	12	Present	Present	Absent
S.M.	2	Pharyngitis	Chloramphenicol	3	Absent	Present	Absent
J.W.	6	Measles	None	8	Absent	Absent	Absent
D.O. (Recurrence)	3¾	Upper respiratory infection Pharyngitis	None	3 3	Present Absent	Present	Absent
M.G.	9	Pharyngitis; ? rheumatic fever.	Sulfonamide	14	Absent	Present	Absent
H.W.	3	Cervical adenitis; pharyngitis.	Chlortetracycline & penicillin	28	Absent	Present	Present
D.F.	3	Tonsillitis & otitis media	None	7	Absent	Present	Present
M.B.	4½	Tonsillitis	Penicillin & chlortetracycline	13	Present	Present	Present
E.S.	2	Upper respiratory infection	Chloramphenicol	4	Absent	Absent	Absent
B.A.J.	10	Upper respiratory infection	None	7	Absent	Present	Absent
J.B.	4	Upper respiratory infection	None	4	Absent	Present	Absent
J.N.	6	Tonsillitis	None	14	Present	Present	Absent
A.K.	2½	Pyuria	Sulfonamide	5	Present	Absent	Absent

MATERIALS AND METHODS

The patients in this series were all children admitted to the wards of the Boston Floating Hospital because of a purpuric eruption. The significant findings are described in Table 1. Blood counts and certain screening tests of the hemostatic mechanism, including bleeding time, coagulation time, clot retraction, prothrombin time of plasma and serum (prothrombin consumption) and tourniquet test, were carried out in all cases. Bone-marrow aspirations were performed in 6 cases, and skin biopsies in 4. Urinalyses, Addis counts, blood cultures, throat cultures, tuberculin tests and determinations of nonprotein nitrogen were performed in all patients.

The patients were followed closely until all manifestations of purpura had disappeared. Most of them were re-examined at follow-up visits to the Hematology Clinic and Laboratory.

The patients ranged in age from two to nine years, and included 9 girls and 6 boys. Among the cases in the literature, there appear to be more males than females.[1,2]

CLINICAL PICTURE

The children were all admitted to the hospital acutely ill, usually complaining of joint pains, fever and malaise in addition to purpura. In all cases, except in 1 in which pyuria was present, there was a

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history of an antecedent infection of the pharynx or tonsils, followed by a period of three to twenty-eight days before the appearance of the purpuric eruption.

Purpura

The skin lesions, which were intensely purple at first, were noted chiefly on the lower back and buttocks, and about the extensor surfaces of the elbows, arms, lower legs, ankles and feet, the trunk being free in all cases. They varied greatly in size — that is, from fine, pin-point lesions to large, extremely purple and somewhat elevated, hemorrhagic spots. There was no blanching with pressure. Occasionally, a few purpuric lesions were noted in the buccal mucosa. The deep-purplish color of most of the lesions, their tendency to coalesce and their great variability in size and shape contrasted with the relatively small, regular and pinkish petechiae of "idiopathic" thrombocytopenic purpura.

In 7 patients the skin lesions began as urticarial wheals accompanied by itching, which became purpuric within a short time. Antihistamine preparations given in a few cases before hospitalization had failed to alter the progress of the lesions. In the remainder of the cases the skin manifestations had begun with purpura.

Joint Symptoms

These occurred in 14 (93 per cent) of the patients, varying from slight aching in a single joint in 1 case to painful swelling of many joints. Although the pain was not usually as severe as that in rheumatic fever, that condition was considered a diagnostic possibility by the referring physicians in 2 cases. As the purpura cleared, the joint symptoms subsided in twenty-four hours to two weeks. During the period of arthralgia, fever was either absent or low grade.

Gastrointestinal Symptoms

These were present in 8 cases (53 per cent), usually occurring early in the course of the disease. The patients complained of severe colicky abdominal pain, and in 6 patients, there was a history of melena for a period of four to nine days. No bright-red blood was noted in the stools of any of the patients in this series. The acute abdominal pain was usually referred to the umbilicus and lasted for one to twenty-six days. As the purpura subsided, all intestinal symptoms disappeared.

TABLE 1 *(Concluded).*

PATIENT	ABDOMINAL PAIN OR MELENA	PHARYNGITIS (SORE THROAT)	FEVER	RED-CELL COUNT AT ONSET	WHITE-CELL COUNT	PLATELETS	EOSINOPHILS
							%
S.C.	Present	Present	Present	3,530,000	6,950	800,000	6
J.M.	Present	Present	Present	3,920,000	19,000	929,000	2
M.R.	Absent	Present	Present	4,000,000	11,600	489,600	2
A.G.	Absent	Present	Present	3,700,000	8,900	817,000	2
S.M.	Present	Present	Present	3,810,000	9,400	526,780	6
J.W.	Absent	Present	Present	4,500,000	10,500	437,500	1
D.O.	Absent	Present	Present	3,650,000	8,100	490,350	3
(Recurrence)	Present		Present	3,500,000	6,900	250,000	2
M.G.	Absent	Present	Present	3,800,000	6,700	601,430	5
H.W.	Present	Present	Present	3,800,000	10,250	1,591,000	10
D.F.	Present	Present	Present	3,120,000	7,500	380,000	2
M.B.	Present	Present	Present	4,400,000	13,800	1,269,840	1
E.S.	Absent	Present	Present	3,620,000	7,250	440,000	2
B.A.J.	Present	Present	Present	4,400,000	10,700	280,000	2
J.B.	(Abdominal pain present; melena absent.)	Present	Present	4,400,000	16,200	340,000	1
J.N.	Absent	Present	Present	3,600,000	10,000	399,500	2
A.K.	Absent	Absent	Present	4,200,000	12,700	625,000	11

Nephritis

Henoch[8] pointed out that nephritis was a frequent complication of this type of purpura, and that it indicated a poor prognosis; in fact, 1 of the 3 patients he described died of renal failure. Osler[4-7] stated that acute glomerulonephritis was the most serious complication of the disorder, 7 of his 33 patients having died of renal failure. Three of our patients showed the features of acute nephritis, including hematuria and albuminuria. In 1, the symptoms and signs of nephritis appeared forty-nine days before the onset of the purpuric eruption of the skin. Evidence of microscopic hematuria persisted for four months in the first case and for fifteen months in the second. When the

third patient (M.B.) was last seen, thirty months after onset, urinalysis revealed no albuminuria or gross hematuria, but an Addis count showed 1,850,000 red blood cells and 411,100 white blood cells per cubic millimeter, but no casts.

These findings indicate that the renal lesion is the slowest to heal and that nephritis in association with purpura may have a graver prognosis than when it occurs alone. Cases of acute vascular purpura and nephritis reported in the literature reveal that at autopsy the pathological picture is the same as that in acute glomerulonephritis.

Hematologic Studies and the Hemostatic Mechanism

The red-cell counts in our series varied between 3,100,000 and 4,500,000, and the white-cell count between 6900 and 19,000. Five patients (33 per cent) had eosinophilia (counts of 5 to 11 per cent). The patient with 11 per cent eosinophils in the peripheral blood also had eosinophilia of the bone marrow. The platelet counts in all patients were within normal limits and in 5 cases were somewhat increased — to over 800,000 (normal 500,000 to 600,000). Bleeding time, coagulation time, clot retraction, prothrombin time and prothrombin consumption were normal in all cases.

Bone-marrow aspiration in patient A.G. showed normocellularity, with an increased number of megakaryocytes and clumps of platelets. Patient M.B. had a normocellular marrow, with a large number of active megakaryocytes and masses of platelets, and a normoblastic erythroid hyperplasia, with a normal number and maturation of granulocytic elements. Patient A.K. had a normocellular marrow, with a large number of megakaryocytes, masses of platelets, granulocytic hyperplasia and eosinophilia. Similar findings were revealed in the marrow of patient J.N.

Possible Etiologic Factors

Years ago Schönlein[8] and Glanzmann[9,10] pointed out that the purpura was often preceded by infection. More recently, Davis[11] discussed the relation between infection and the development of the purpura. All 15 of our patients had a history of an upper respiratory infection occurring three to twenty-eight days before the appearance of purpuric lesions; in 1, there was a history of an infection of the urinary tract as well. Most of the infections were accompanied with sore throat, but in only 1 patient (J.N.) did the throat culture reveal beta-hemolytic streptococci. In all cases, blood cultures were negative. The negative throat cultures may have been due largely to the fact that in 10 cases, therapy with one or another antibiotic had been given before hospital admission. In one patient, purpura followed an attack of measles, which had occurred 8 days previously.

Only 3 patients in our series gave a positive family history of allergic disorders such as asthma, hay fever and eczema. Bartley and Bell[12] and also Gairdner[2] found no undue frequency of a positive family history of allergy among their cases. One of our patients (J.W.) had had asthma and a history of a previous sulfonamide sensitivity reaction; in another (M.B.) penicillin sensitivity had developed at two and a half years of age. Alexander and Eyermann[13] reported a series of cases of purpura and abdominal pain due to hypersensitivity to various foods; these cases differed from Schönlein–Henoch purpura in several respects.

Histologic Findings

Skin biopsies were performed in 4 cases.

In D.O. a section of skin showed an intense focal acute inflammatory reaction about the capillaries of the superficial corium, consisting of numerous polymorphonuclear leukocytes, lymphocytes and histiocytes densely packed about the involved capillaries. Eosinophils were inconspicuous. There was a thickening of the involved capillary walls and swelling of endothelial cells, resulting in great narrowing of the affected capillaries. Some capillaries were completely occluded by these changes. An extravasation of erythrocytes into the perivascular edematous areas of the involved vessels was noted. There were no thrombotic occlusions of the vessels, and no fibrin or collagen necrosis was found in the inflammatory areas. The lesions appeared to vary in age, the older ones being characterized by absence of edema, densely packed cells and pyknotic nuclei.

In H.W. the deeper capillaries did not appear to be involved in vessels close to the epidermis. A perivascular exudate of polymorphonuclear leukocytes, lymphocytes, occasional eosinophils and erythrocytes was noted. The endothelial cells were swollen. No collagen necrosis or capillary thrombosis was observed. This case showed the least involvement.

In D.F.,[14] who showed the most marked changes, the collagen was uniformly stained. There was perivascular exudation of polymorphonuclear leukocytes, together with a few eosinophils, lymphocytes, histiocytes and also edema. Thickening of the capillary walls was present, with swelling of the endothelial cells and slight extravasation of erythrocytes into the lesion. These vascular changes, which involved both capillaries and small arterioles, were found throughout the corium. No intravascular thrombosis was seen and no areas of necrosis of the vessel wall were noted (Fig. 1 and 2).

A second biopsy, taken after a course of ACTH therapy, demonstrated striking improvement. The vessels and the superficial corium showed only minimal infiltration of lymphocytes. No abnormality of the capillary or arteriolar walls was noted, and no necrotic lesions were seen.

In M.B. a perivascular exudate of polymorphonuclear leukocytes, lymphocytes and erythrocytes forming a cuff along segments of the capillaries was evident. A few eosinophils were found in the exudate. The lumens of the capillaries were narrowed by

swelling of the endothelium; swelling of the capillary wall was noted. These involved vessels were found close to the epidermis in the papillae of the corium. No changes in the epidermis, collagen or glands and no capillary thrombosis were seen.

Thus, an acute inflammatory reaction involving the capillaries was evident in all 4 cases in which biopsies were done. A variable cuff consisting of polymorphonuclear leukocytes, lymphocytes, histiocytes and edema and eosinophils in small numbers was found. There was swelling of the endothelial cells. Edematous thickening of the capillary wall was found. About many of the lesions there was an extravasation of erythrocytes into the surrounding tissue. The lesions, although found in all areas of the skin, were mostly located in the superficial corium. However, in the

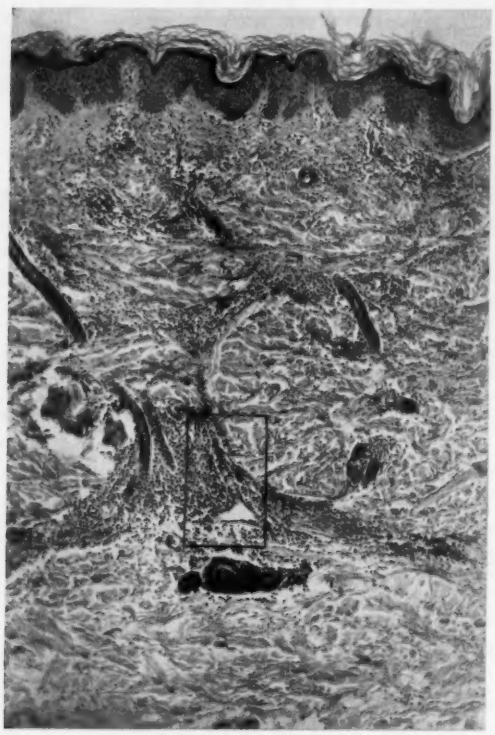

FIGURE 1. *Photomicrograph in Patient D.F., Who Had the Severest Type of Histologic Reaction (X75).*
Note the inflammatory exudate about the arterioles in the lower portion of the vessels and skin appendages.

severest cases the small arterioles were also surrounded by this inflammatory exudate.

Important negative findings were the absence of necrosis or changes in the collagen fibers, absence of fibrin in the inflammatory lesion, absence of thrombi in the capillaries and no necrosis of vessel walls. The use of periodic acid-Schiff stains, elastic-tissue stains and Mallory aniline blue stains gave no further information.

TREATMENT

When any active focus of infection was found, treatment with the appropriate antibiotic was instituted.

Because of the dramatic results noted in certain autoimmune and allergic conditions treated with ACTH, 3 patients who were apparently not improving on conservative treatment were given a course of ACTH therapy for fourteen days. Within a week, the purpuric lesions disappeared in all. In 1 case (D.F.) a second skin biopsy after fourteen days of treatment revealed almost complete regression of the perivascular lesion. In this case new purpuric lesions appeared a week after cessation of therapy but receded spontaneously.

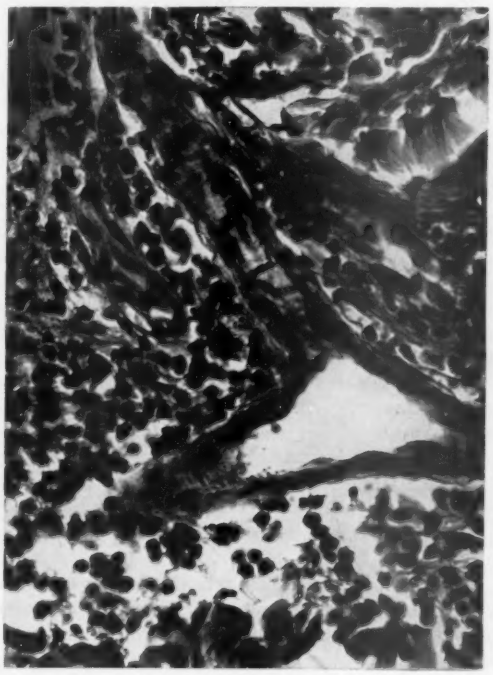

FIGURE 2. *Magnification of the Square Inset in Figure 1 (X240).*
Note the cellular infiltration about the arterioles.

DISCUSSION

Acute vascular purpura is a polymorphous disease characterized by urticarialike and purpuric skin lesions usually associated with other hemorrhagic manifestations involving joints, gastrointestinal tract and kidneys. The various features may be concomitant or may appear as isolated symptoms. As a result, the clinical picture is extremely variable. The skin purpura may be construed as simply one of the manifestations of a generalized disturbance involving the small blood vessels. The fundamental lesion is apparently a vasculitis and perivasculitis. The joint

symptoms appear to be due to periarticular edema similar to that seen in serum sickness, an allergic disease. Gastrointestinal symptoms and melena are probably due to hemorrhage and edema on the basis of vascular lesions occurring in the wall of the intestines. Such lesions have been described at laparotomy in cases in which an operation was performed in the mistaken assumption that an acute abdominal emergency was present. Involvement of the glomeruli adequately explains the glomerulonephritis and often marked hematuria. The diagnosis of acute vascular purpura should be considered in every case in which any of the acute symptoms develop, whether alone or together, a few days to two weeks after the occurrence of an infection.

The occurrence of a preceding infection followed by a latent period before the onset of the vasculitis in all our cases appears of definite significance. It is possible that the infection is responsible for the initiation of an immunologic response. After a latent period of incubation, an antigen-antibody reaction at the vascular level might be responsible for vascular damage and thus for the histologic lesions observed in this disease.[15] The role of the beta-hemolytic streptococcus in this mechanism remains to be explained. The importance of the hemolytic streptococcus in initiating the hypersensitivity reaction is well established in rheumatic fever and glomerulonephritis — diseases perhaps based on a similar pathogenic mechanism.

That Schönlein–Henoch purpura is a generalized vascular disease of immunologic origin is indicated on several grounds. Thus, Japanese workers particularly[16,17] and others[18] have reproduced the typical clinical and histologic lesions experimentally with the use of heteroimmune antiblood-vessel serums. The generalized character of the disease, the angiitis and the perivascular changes of the skin found at biopsy are some of the features in common with the "collagen" disorder periarteritis nodosa, which is generally considered to be of immunologic origin. Indeed, some authors[19] have stated that from the histologic standpoint it is difficult in some cases to state where acute vascular purpura ends and periarteritis begins. It is possible that these conditions represent similar disturbances but with involvement of different types of blood vessels, the larger blood vessels being affected in periarteritis. Of importance, too, is the recognition that the disease is by no means simply a skin disturbance, but one with widespread involvement of blood vessels and endothelial surfaces throughout the entire body. Because of location, the renal lesion is by all odds the most serious, and potentially the most important.

Summary and Conclusions

Fifteen cases of acute vascular purpura are discussed. Infection preceded the onset of purpura in all.

The latent period between remission of the infection and the appearance of purpura may be the time during which, in response to an antigenic stimulus of unknown nature, an immunologic mechanism develops. An immunologic "storm," with an antigen-antibody reaction at the end organ (small blood vessels), probably determines the picture of acute inflammatory perivasculitis found in the walls of the small blood vessels of the corium, capillaries of the synovia, glomeruli of the kidney and small blood vessels of the walls of the intestines and in turn explains the varied symptomatology.

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Correction: On pages 723 and 724 of the paper by Drs. Slayton, Burrows and Marble entitled "Lente Insulin in the Treatment of Diabetes," which appeared in the October 27 issue of the *Journal*, the present Figure 2 should be Figure 3, and the present Figure 3 should be Figure 2, the legends remaining unchanged.

MEDICAL PROGRESS

EMERGENCE OF ANTIBIOTIC-RESISTANT BACTERIA (Concluded)*

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BIOLOGIC AND BIOCHEMICAL PROPERTIES OF ANTIBIOTIC-RESISTANT STRAINS

Comparisons of Sensitive and Resistant Strains of the Same Species

Although the mechanisms involved in the development of antibiotic resistance will not be considered in detail, some studies designed to elucidate the problem and some illustrations of differences between sensitive and resistant strains may be mentioned. Bellamy and Klimek[473] noted that a penicillin-resistant variant of *Staph. aureus* grew more slowly than its sensitive parent culture and also lost its ability to grow anaerobically. They could not increase significantly the resistance of strains of *Str. faecalis, Str. mastitidis* or *Clostridium welchii* by similar methods. They suggested that organisms that depend on anaerobic processes for their energy supply will not become appreciably resistant to penicillin. Changes in metabolic activities and growth requirements of streptomycin-resistant organisms have also been reported by many workers,[474-477] but streptomycin-inactivating substances could not be demonstrated in such organisms or their products.[476] Anderson[478] pointed out a number of metabolic and biochemical changes in a strain of staphylococcus isolated from a patient and found to be resistant to 5 antibiotics; some of these changes had also been described in strains made highly resistant in vitro. Alexander and Leidy[479] induced streptomycin resistance in *H. influenzae* by exposing sensitive strains to extracts of resistant ones; this was shown to be associated with transfer of desoxyribonucleic acid (DNA) from the resistant strain in the same manner that Hotchkiss produced penicillin-resistant strains of pneumococci[480] and other streptomycin-resistant organisms.[481] Without consideration of the details of the genetic aspects,[6,7,9] it is now recognized that most organisms acquire resistance stepwise by grades that vary for different antibiotics and different species. However, high degrees of resistance to streptomycin — and also to isoniazid and occasionally other agents — may emerge suddenly in a single stage. Kaipainen,[482] for example, demonstrated completely penicillin-resistant variants of 2 originally sensitive strains of *Bacillus subtilis* after a single cultivation in broth containing penicillin. Both the stepwise and the single large-step types of resistance have been observed to develop simultaneously by several workers.[287,483,484]

Beljanski,[485,486] comparing streptomycin-resistant and streptomycin-sensitive variants of the same strains of *Staph. aureus* and *Esch. coli,* found that the latent phase of growth of the resistant strains was more prolonged than in the corresponding sensitive strains and they accumulated more ribonucleic acid, and only this substance, at the end of the latent phase. Other constituents showed no difference; these incuded proteins, orthophosphates, ribose and desoxyribose nucleotides and desoxyribonucleic acid. A penicillin-resistant variant of the same strain of *Staph. aureus* accumulated not only ribonucleic acid but also proteins, purine nucleotides and phosphorolated acid-soluble compounds. Penicillin was considered not to interfere with depolymerization of ribonucleic acid, which degrades and then participates in protein synthesis. Streptomycin, on the other hand, combines with ribonucleic acid (or with nucleoproteins) and prevents its depolymerization. A sulfonamide-resistant *Staph. aureus* exhibited a prolonged latent period during which it accumulated twice as much desoxyribonucleic acid as its sensitive parent; this was in contrast to the streptomycin-resistant and penicillin-resistant variants, which accumulated more ribonucleic acid and not desoxyribonucleic acid. Streptomycin-resistant strains of *S. enteritidis*[486] behaved differently from the other species; they were richer in desoxyribonucleic acid than their sensitive parents. Rates of multiplication of the resistant variants did not depend on the amounts of ribonucleic acid.

Hobson[487] could establish no change in the properties of erythromycin-resistant strains as compared with their parent erythromycin-sensitive strains, except slower growth and crossresistance to carbomycin.

Eagle,[488] using isotopically labeled penicillin, demonstrated that, in addition to extracellular penicillinase production, by which bacteria convert penicillin to penicilloic acid, or, as in 1 instance, dependence on penicillin for multiplication, there are at least 3 mechanisms of penicillin resistance: a number of strains degrade penicillin after it enters the cell — this was found in *Esch. coli, P. morganii* and *Shigella paradysenteriae;* the resistant strains bind less penicillin than the sensitive ones; and, by some unknown mechanism, cells of penicillin-resistant variants of normally sensitive strains may combine with penicillin to the same degree as the cells of the parent sensitive strains without being killed.

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Antibiotic-resistant variants may arise as a result of environmental factors other than exposure to the antibiotic. Thus, Smolens and Vogt[489] found a greater proportion of streptomycin-resistant cells in cultures of *H. pertussis* or *M. aureus* grown on Cohen–Wheeler medium as compared with parallel cultures from the same suspension grown on Bordet–Gengou medium. The latter, they found, could also substitute for streptomycin as a nutritional source for a streptomycin-dependent strain of *H. pertussis*. A marked increase in resistance of staphylococci to penicillin and streptomycin was reported to follow promptly after ultraviolet irradiation.[490] Such large increases in resistance could not be confirmed in *Esch. coli* by Saz et al.[491] after irradiation of either the culture or the medium before inoculation; they did, however, note a striking increase in the proportion of irradiated cells that were of intermediate resistance to streptomycin (4 to 10 microgm. per cubic centimeter). Szybalski[492] also claimed to have developed streptomycin resistance by exposure to the antibiotic without multiplication of the organisms; if confirmed, he believes this may be the first real demonstration of "Lamarckian" inheritance.

Saz and Eagle[493] plated out varying numbers of *M. aureus, Str. pyogenes* and *Diplococcus pneumoniae,* Type III, on agar containing threshold concentrations of penicillin and found that the emergent number of colonies paradoxically decreased as the size of the inoculum increased. The weakly resistant organisms that would normally grow out became nonviable in the presence of large numbers of bacteria dying under the impact of the antibiotic. This phenomenon occurred only irregularly with *Str. faecalis* and was not observed with a strain of *Esch. coli.* When highly resistant organisms (*M. aureus, Str. pyogenes* or *D. pneumoniae*), derived from an initially sensitive strain by serial transfer through penicillin, were plated with large numbers of the parent sensitive strains in low concentrations of penicillin, the resistant strains failed to grow out. This phenomenon was strictly specific. The mechanism may be related to the transformation through the release of desoxyribonucleic acid from the sensitive cells, as described by Hotchkiss.[430]

Changes in colonial and microscopical morphology of streptomycin-resistant strains have been noted by several groups of workers.[494-496]

Espersen[497] found that strains resistant to streptomycin in vivo as well as highly resistant variants derived from sensitive cultures of *Myco. tuberculosis,* were indistinguishable in morphology and rate of growth both in microcultures and in Dubos's medium. Penicillin has the same bacteriostatic and bacteriolytic effect, and sulfathiazole had the same bactericidal effect on sensitive strains on both types of streptomycin-resistant strains. Streptomycin resistance was therefore considered to be highly specific. Espersen[498] could not demonstrate the production of "streptomycinase" during the growth of a strain of tubercle bacillus that was not inhibited by 2000 microgm. of streptomycin per cubic centimeter. He[497] and others[499] were able to demonstrate highly resistant variants in cultures of sensitive strains not previously exposed to streptomycin.

Differences in the metabolism of streptomycin-sensitive and streptomycin-resistant variants of H37Rv, the human virulent strain of *Myco. tuberculosis,* were described by Peterson and Pope.[500] Both variants synthesized all components of the vitamin B complex, but there was a slight increase in the synthesis of inositol, histidine and tryptophan and an increase in the amount of leucine, isoleucine and valine produced by the resistant variant that could not be accounted for on the basis of differences in growth. The growth requirement of isoniazid-resistant strains of *Myco. tuberculosis* were studied by Barry et al.,[501] and some of them were found to be unpredictable.

Persistence of the Resistant Trait

Two types of penicillin resistance have been described among staphylococci,[4,86,170] one that is temporary and follows exposure of sensitive organisms to increasing concentrations of antibiotic in vitro[170] and another that is permanent and is observed in strains obtained from infected sources; only strains of the latter type produce the penicillin-destroying enzyme, penicillinase. Other workers,[84,502,503] however, have derived penicillinase-producing strains of staphylococcus from originally penicillin-sensitive strains during exposure to the antibiotic and also obtained strains that do not produce penicillinase from resistant and penicillinase-producing ones during exposure to other antibiotics.[82] These and other studies on the resistance of the staphylococcus have been reviewed by Barber,[84] and those on the resistance of other organisms by Pollock[504] and Abraham.[505]

Barber[81] obtained penicillin-sensitive strains from a varying and often major proportion of resistant and penicillinase-producing strains isolated from patients, depending on the medium used, the period of incubation and the number of subcultures. She could not accelerate the reversion to sensitivity by exposure to x-rays or by growth with other organisms. Chandler et al.[506] demonstrated a loss of penicillinase production in staphylococci on exposure to sublethal concentrations of chlortetracycline, and Barber,[82] likewise, could select out penicillin-sensitive strains from originally resistant penicillinase producers by serial subcultures on agar plates containing streptomycin or chloramphenicol. Graessle and Frost[494] demonstrated reversion to sensitivity of strains made resistant to penicillin or streptomycin in vitro by repeated subcultures in antibiotic-free mediums. Others[483,507] accomplished this only irregularly and with difficulty in organisms that were highly resistant to streptomycin. Still others[288,294,508] failed to demonstrate changes in resistance over long periods, and Miller and Bohn-

hoff[508] continued to culture streptomycin-resistant strains in the nasopharynx of 1 patient for a whole year.

In another study, Barber[83] developed 4 types of resistant variants from an originally sensitive strain of *M. aureus*. One of these types was resistant and grew equally well with or without penicillin, and the second was resistant but grew less well in the presence of penicillin; the third formed minute colonies that were much more resistant than the parent, and the fourth was a penicillin-dependent variant, unstable and growing best in a narrow range of penicillin concentrations. Whereas the first two forms increased in resistance by gradual stages, the third increased by a single stage and retained the same resistance. The latter type of colony was, morphologically at least, similar to the small-colony type isolated by Wise and Spink[88] from patients under treatment with penicillin. Small-colony variants (G forms) that are highly resistant to penicillin were reported earlier by Schnitzer et al.,[509] who isolated some of them on penicillin-containing agar and others after exposure to barium chloride; all these strains were also resistant to methyl violet. Youmans et al.[510] also produced small-colony variants of *Staph. aureus* on exposure to penicillin; these were unstable, as were those of Wise and Spink.[88]

Weinstein and Tsao[511] were able to increase the penicillin resistance of *Str. pyogenes* only slightly by serial subcultures in penicillin-containing mediums. This resistance was only temporary and was readily abolished by frequent subcultures in antibiotic-free mediums.

Virulence of Resistant Variants

Wide differences have been found among Types 1, 2 and 3 pneumococci in the degree of resistance that they develop on exposure to penicillin; the increased resistance was associated with a loss of virulence that could not be restored by serial passage through mice.[512] Resistance of a strain of *Staph. aureus* could not be increased by passage in mice in the presence of penicillin.[512] Strains of meningococci made resistant to penicillin in vitro, however, retained their virulence for mice, and large doses were required to protect them against infection with such resistant strains.[513] Observations on the virulence of drug-resistant strains of *Myco. tuberculosis* were included in an earlier section.

Penicillin-resistant strains of staphylococci and streptococci were made sensitive by growth in mixed cultures with other organisms that were sensitive. This was accomplished by Voureka[514] even if the bacterial association occurred in the refrigerator where growth did not take place. Some bacterial autolysates could also affect the change, and the sensitivity thus acquired was a lasting one. Winner[515] confirmed Voureka's findings and succeeded in increasing the penicillin sensitivity of a relatively resistant staphylococcus some 200-fold by growing it for four hours in contact with a sensitive streptococcus, which became relatively resistant to penicillin after this treatment. Bennison and Schwabacher,[516] on the other hand, failed to confirm Voureka's findings; they observed a loss of resistance on standing without exposure to penicillin, but this was reacquired by transfer in increasing concentrations of the antibiotic. Fairbrother et al.[517] isolated both sensitive and resistant staphylococci from 6 of 200 apparently resistant cultures isolated from infectious processes. Growth of these 6 strains together with *Str. hemolyticus* or in the presence of other antibiotics did not appear to influence the natural development of the sensitive variants.

Seligmann and Wassermann[476] demonstrated some loss of mouse pathogenicity in strains of salmonella accompanying the development of streptomycin resistance. Chandler and Schoenbach,[483] on the other hand, noted no change in the original virulence of resistant strains of various organisms for human blood. The streptomycin-resistant meningococci produced by Miller and Bohnhoff[518] retained their virulence, and this was accompanied by failure of streptomycin to influence the infection of mice with such resistant organisms. Mice pretreated orally with streptomycin were found by these workers[375,376] to be more susceptible than normal mice to infection with streptomycin-resistant *S. enteritidis*.

Antibiotic-Dependent Bacteria

From cultures of a streptomycin-susceptible meningococcus on streptomycin-containing agar, Miller and Bohnhoff[508,519] obtained two types of resistant colonies; one grew equally well in the presence or absence of streptomycin, which is the usual "resistant" type, and the other grew only in the presence of the antibiotic and was therefore "streptomycin-dependent." These two types of colonies differed in appearance and were readily distinguishable. The optimum growth of the dependent variant occurred in a narrow range of concentrations (100 to 400 microgm. per cubic centimeter). Streptomycin-dependent organisms have since been isolated in vitro by many workers[329,375,475,496,520-524] from a large variety of bacterial species including *M. aureus, Esch. coli, Ps. aeruginosa, P. morganii, S. typhosa* and other species of salmonella, *A. aerogenes, H. influenzae*, shigella, *B. subtilis* and brucella. Alexander and Leidy[475] also observed some strains of *H. influenzae* that grew better in the presence of streptomycin in the medium, and Hobby and Dougherty[525] described a dependent variant of a pseudomonas-like strain that apparently could multiply in an aqueous solution of streptomycin without addition of other nutrients. Hall and Spink[255] isolated a streptomycin-resistant strain of *Br. abortus* from the blood culture of a patient under treatment with this antibiotic and noted that its growth was stimulated in vitro by the addition of a sublethal concentration of

streptomycin. The four types of resistant variants of *M. aureus* developed by Barber[83] have already been mentioned.

In general, streptomycin dependence is not associated with changes in susceptibility to other antibiotics, but Yegian and Budd[526] described a strain of *Myco. ranae* that was resistant to sulfathiazole when streptomycin dependent. Dependent variants have also been isolated from the throats of patients under treatment with streptomycin and, along with resistant strains, among the usual inhabitants of the throat and large bowel of mice and rabbits after oral administration of large doses of the antibiotics.[326,327] Stenderup[295] also cultured streptomycin-dependent strains from the infected urine of 8 patients under treatment; some of them persisted for several days after the streptomycin was withdrawn. In 1 of these cases the infection was aggravated when therapy with streptomycin was resumed.

Paine and Finland[496,520] found that the concentrations at which optimum growth of streptomycin-dependent variants occurred was critical and varied with the strain; during prolonged growth at higher or lower concentrations of streptomycin, mutations back either to resistant or to sensitive variants or to both took place. This was confirmed by Stenderup.[527] The streptomycin-dependent meningococci of Miller and Bohnhoff,[508] however, appeared to be quite stable, but those of Rake[521] were not so stable. The dependent variants differed both in colonial and microscopical morphology from the parent sensitive strains, especially when grown for long periods in suboptimal concentrations of streptomycin.[375,508,519]

The streptomycin requirement of the streptomycin-dependent variant is so specific that its use has been recommended as a test of streptomycin production by bacteria,[528] but this may not apply to all bacteria, for it has already been noted that Bordet–Gengou medium was found to serve as a nutritional source for a streptomycin-dependent strain of *H. pertussis*.[489] Streptomycin-dependent strains will not survive in the presence of hydroxylamine or cysteine, which inactivates streptomycin; however, certain conjugated streptomycins and other derivatives, according to Rake[521] and Winsten,[529] may replace streptomycin for growth of dependent strains. In animals, infection with streptomycin-dependent organisms does not take place unless they are treated with streptomycin. Olitzki and Sulitzeanu[530] found that streptomycin-dependent brucella did not produce infections in human volunteers, but they induced low-grade antibody titers temporarily,[528,530] and these workers considered using them for vaccines.[530] However, they were deterred by the possibility of reversion to virulent and nondependent forms in vivo, such as occurs in vitro.

Mention was made earlier of the isolation of antibiotic-dependent organisms from infected urine. Schiøtt and Stenderup[296] isolated 8 strains of gram-negative, nonlactose-fermenting bacilli that formed greenish, pyocyaneus-like colonies and were partially dependent on chlortetracycline, oxytetracycline and chloramphenicol. These differed from the usual dependent variants in that they were sensitive to both low and high concentrations of the antibiotics but grew best only in the presence of intermediate concentrations. They were also partly dependent on more than one antibiotic and grew well in suitable mediums in the absence of these antibiotics. Only 2 of the 8 strains were from patients who had received treatment with oxytetracycline, whereas the others had not received any antibiotics. The patients had all had surgical procedures performed on their urinary tracts, and their infections were considered to be nosocomial.

Strains of organisms truly dependent on any of the commonly available antibiotics other than streptomycin have rarely been encountered clinically, and except for streptomycin and penicillin, have not been readily developed in vitro. However, Gocke and Finland[531] reported the isolation of a chloramphenicol-dependent variant of a strain of *K. pneumoniae* during serial subcultures in the presence of increasing concentrations of this agent. This strain was unstable, giving rise to both normally sensitive and resistant variants, growing best at an optimum concentration of chloramphenicol and not at all in its absence. Its growth was not supported by any other generally available antibiotic.

The subject of streptomycin-dependence in organisms other than tubercle bacilli was reviewed in 1949 by Miller and Bohnhoff.[8] They pointed out, as others have, that to determine whether streptomycin dependence is contributing to a therapeutic failure it would be necessary to inoculate infected materials from the patient simultaneously on streptomycin-containing agar and on antibiotic-free agar. If more colonies develop on the former, subcultures of colonies from that medium, when again planted on both mediums, will reveal which are dependent and which are resistant.

Streptomycin-dependent tubercle bacilli have been observed clinically. Spendlove et al.[532] observed that growth of a culture of tubercle bacilli from the same sputum was much greater on a culture containing streptomycin than in a control tube. The sputum was obtained on the ninety-sixth day of streptomycin therapy, and there was rapid progression of the disease at the time. Subsequently, they again obtained a specimen from the same patient and got similar results; tubercle bacilli did not grow without streptomycin and grew well when this was added to the culture medium. Owen et al.[175] observed a similar case; after streptomycin therapy was stopped, streptomycin-sensitive organisms were again obtained from their patient.

Doane and Bogen[533] developed a strain in vitro that required streptomycin in the medium for growth; this property was maintained through succeeding subcultures. This strain, however, did not produce disease when inoculated into guinea pigs,

with or without streptomycin therapy. A streptomycin-sensitive mutant derived from it, however, was fully virulent for guinea pigs. In contrast to Wolinsky and Steenken,[200] who failed to develop resistant strains during prolonged treatment in mice, guinea pigs or rabbits, Lenert and Hobby[534] obtained strains that were highly resistant and also dependent from cultures of 6 out of 196 mice infected intracerebrally with the H37Rv strain of *Myco. tuberculosis*. On passage in mice, they could culture only streptomycin-resistant and streptomycin-dependent strains. Only 2 of the 6 strains were as virulent as the parent strain from which they were derived; the others were of low virulence, causing death of mice in three to six months, with many surviving longer than six months. Virulence was not enhanced by treatment with streptomycin. The strains that were virulent were found to be sensitive to streptomycin in vitro.

Yegian and his co-workers[526,535-537] isolated a streptomycin-dependent variant from a sensitive strain of *Myco. ranae*. They could also isolate streptomycin-dependent variants in a single culture after prolonged incubation of *Myco. tuberculosis* and *Myco. ranae* on mediums containing 100 microgm. of streptomycin per cubic centimeter, and they could derive the dependent variant from a resistant population, but on subculture they obtained both sensitive and resistant progeny and the dependent strain grew best in an optimum concentration of streptomycin. When the dependent strain was grown together with resistant ones for several subcultures, the former variant could no longer be detected. From a pigment-producing species of mycobacterium, Yegian and Budd[537] isolated two distinct types of streptomycin-dependent variants; these segregated on subculture into other mutants, which then bred true, the progeny being either streptomycin-sensitive or streptomycin-resistant, and each of these was stable.

Crossresistance

Numerous in vitro studies of the development of crossresistance — that is, resistance to other antibiotics than the ones to which organisms have been exposed — have been reported.[141,387,538-551] In 1946, Eisman, Marsh and Mayer[550] reported that a strain of *Staph. aureus* made resistant to penicillin F, G or X in vitro, showed similar resistance to each of the other penicillins. Dowling, Hirsh and O'Neil[551] also accomplished this in a number of strains of different species freshly isolated from patients and showed parallel rises in resistance to penicillin F and G after subcultures in either one; they also noted a strain of *Str. viridans* and one of *Staph. aureus* from cases of bacterial endocarditis in which successive strains isolated from blood cultures showed increasing resistance to penicillin during therapy, the resistance to both penicillins G and X rising in parallel. All studies have indicated that strains made resistant to one of the tetracyclines also acquire resistance to the others, and there is some, but less marked, crossresistance between these antibiotics and chloramphenicol; no crossresistance but occasional increased sensitivity to streptomycin has been noted in such strains. In burn wounds, however, crossresistance between chlortetracycline and oxytetracycline was demonstrated in staphylococci by Thompson et al.[545] in patients treated with chlortetracycline, but crossresistance to chloramphenicol was not observed in these strains.

Kaipainen[540] studied crossresistance in 37 strains of 5 species after a few transfers of each in broth containing one of 5 antibiotics (penicillin, dihydrostreptomycin, chlortetracycline, oxytetracycline and chloramphenicol) and obtained uniform results with gram-negative bacilli, but the results with gram-positive organisms were variable. He observed no crossresistance in either direction between penicillin and any of the other 4 antibiotics. Monnier and Schoenbach[543] could demonstrate no change in sensitivity to polymyxin B in strains made resistant to any of these 5 antibiotics. Vaisman and Henry-Eveno[549] noted variations both in the degree of homologous resistance developed from exposures to chloramphenicol and chlortetracycline and in the crossresistance between these antibiotics to oxytetracycline and penicillin, depending on the species. They noted crossresistance to penicillin as well as to chlortetracycline and oxytetracycline in a strain of *S. typhosa* and in a staphylococcus that had been made resistant to chloramphenicol, and they also demonstrated an increase in resistance to penicillin from 5 to 100 units per cubic centimeter in a strain of *P. vulgaris* that had been exposed to chlortetracycline. Crossresistance in varying but not marked degrees between streptomycin and neomycin has also been noted repeatedly.[538,542,544,546,547]

Although crossresistance between streptomycin and neomycin was observed by Haight et al.,[387] crossresistance of streptomycin-resistant strains to other common antibiotics was not observed by Alexander and Leidy[475] or by others. Graessle and Frost,[494] however, reported 2 strains of staphylococcus that acquired some increase in streptomycin resistance as they increased in resistance to penicillin, but the reverse was not observed — that is, the streptomycin-resistant strains remained sensitive to penicillin. Miller and Bohnhoff[8] noted that streptomycin resistance can sometimes be accompanied by increases in sensitivity to penicillin.

Andrieu et al.[552] studied the resistance and crossresistance acquired in vitro by 6 strains of *Staph. aureus* exposed to penicillin, streptomycin, chlortetracycline, oxytetracycline and chloramphenicol. They confirmed the clear crossresistance between chlortetracycline and oxytetracycline in every instance and between each of these and chloramphenicol in the only strain that became resistant to the latter. In the others, the sensitivity to each agent remained essentially unchanged after resistance developed to a different one.

Complete crossresistance between erythromycin and carbomycin was demonstrated by many workers.[148,149,487]

Szybalski[553-556] studied the crossresistance patterns of several species of organisms to a large number of antibiotics, using a gradient plate technic that he devised.[557] When strains of *Esch. coli* were made resistant to 15 antibiotics,[553] the resulting crossresistance patterns fell into 4 groups. In Group 1, strains resistant to streptothricin, viomycin, vinactin, catenulin and neomycin showed crossresistance with each other and were also resistant to the streptomycins, but the inverse relation did not hold. There was also crossresistance and crossdependence between streptomycin, dihydrostreptomycin and hydroxystreptomycin. In Group 2, chlortetracycline, oxytetracycline and chloramphenicol were closely related; penicillin and netropsin were less closely related. In Group 3, polymyxin B and circulin showed crossresistance, and bacteria resistant to these 2 also showed one-way crossresistance to some of the Group 1 antibiotics. Group 4 contained only bacitracin. Collateral sensitivity — that is, 100-fold increase in sensitivity to polymyxin B — occurred in one of the strains simultaneously with a 300-fold increase in resistance to chloramphenicol.

A similar study was carried out with *Staph. aureus* and 34 antibacterial drugs.[554] Of those in common use or generally available, polymyxin B, neomycin and viomycin showed crossresistance to each other and also to the streptomycins. Oxytetracycline and chlortetracycline formed a second group with complete crossresistance. Some poorly growing, penicillin-dependent staphylococci and partially chloramphenicol-dependent strains were also isolated in this study.

Myco. ranae was studied with 28 antimycobacterial agents,[555] many of which were not of clinical importance. Among the available ones polymyxin B, viomycin, neomycin and streptomycin were placed in one group, but in this group *Myco. ranae* exhibited a higher degree of selectivity than other organisms. In Group 2 were chlortetracycline and oxytetracycline. In Group 3, chloramphenicol and bacitracin showed crossresistance, and penicillin showed low and not significant degrees of crossresistance with others of this group. Isoniazid and iproniazid were also in a separate group.

Patterns of crossresistance were also studied for a spore former, *B. megaterium*,[556] 44 antimicrobial drugs being used. The only important groupings among the clinically useful ones that evolved were as follows: the streptomycins, neomycin, viomycin and polymyxin G; and the 3 tetracyclines and, to a lesser extent, erythromycin and carbomycin. These studies, in general, confirmed those of others carried out with other technics, except for some of the findings with *Myco. ranae* and some others that were aberrant. They also confirmed the variable results depending on the strains used as well as among the different antibiotics. In general, crossresistance has been found to be most complete and most regular between antibiotics that are closely related in chemical structure[558] but it may depend on similar metabolic properties related to chemically different fractions that are not readily predictable but have generally been worked out only retrospectively.[559]

Antibiotic Combinations and Resistance

The effect of combinations of antimicrobial agents on the rate of emergence of resistant tubercle bacilli has already been considered in an earlier section. The effect of exposure of other bacteria to combinations of antibiotics on the resistance to each agent and to the combinations has also been studied by some workers.

Kaipainen[560] found that in vitro the development of increases in resistance of gram-negative bacilli to chlortetracycline and oxytetracycline resulting from exposures to these agents may be accompanied by a decrease in resistance to dihydrostreptomycin, and, conversely, increasing resistance to dihydrostreptomycin may slightly lower the resistance to the other 3 antibiotics. Using combinations of dihydrostreptomycin with each of those 3 antibiotics, he demonstrated at least partial inhibition of the increase of resistance of *Esch. coli* with all combinations. The proper mutual concentrations of the components in the combination were essential to achieve this effect.

In the study by Monnier et al.,[552] cited above, all the various combinations, in pairs, of the antibiotics they investigated failed to reveal any antagonism, and the effect of each was independent of the other in only 2 strains. In the majority of cases, the pairs of antibiotics used together were either additive or slightly synergistic in their action and this varied with the strain and with the combination of agents. Combinations containing penicillin diminished the risk of acquiring resistance to the individual components of the pair. In strains of staphylococci that produce penicillinase, they noted an appreciable but transient increase in sensitivity to penicillin. Combinations of chlortetracycline, oxytetracycline and streptomycin did not depress or delay the appearance of resistance, but the first 2 of these agents, used together, caused an apparent increase in the risk of developing resistance to these agents, associated with crossresistance between them. Chabbert and Véron[561] found erythromycin and bacitracin to be the most effective bactericidal combination against "polyresistant" staphylococci; penicillin combined with bacitracin and penicillin together with erythromycin were also bactericidal for such staphylococci.

Stenderup[562] noted that the development of resistance to streptomycin could be delayed by sulfathiazole and that sensitivity to streptomycin could be increased by growth in subinhibitory concentrations of sulfathiazole.

The use of combinations of agents to delay emergence and depress the degree of resistance to indi-

vidual agents in vitro was studied by another group of workers.[546,547,563,564] Combinations of erythromycin with either penicillin or streptomycin were found to be effective for this purpose although occasional strains of staphylococci acquired moderate resistance to one or both of these agents while exposed to the pair.[563] Resistance to the same mixtures of antibiotics to which the organisms were exposed also increased, but less than that to the individual components.[546,547,563] It was necessary that the strain be susceptible to both constituents of the pair to achieve any favorable effect since the presence of even a large concentration of penicillin did not delay or depress the resistance to streptomycin or erythromycin resulting from exposure of staphylococci that were originally highly resistant to penicillin.[564] When resistance increased to one of a pair of antibiotics appreciably more than to the other, the resistance to the pair corresponded more closely to that of the antibiotic that produced the smaller change.[546,547] Strains of *Esch. coli* exposed to pairs of antibiotics also generally developed resistance more slowly and to a lesser degree than when strains were exposed to the same antibiotics individually, but there were variations related both to the strains and to the antibiotics used.[547]

The effect of antibiotic combinations in depressing the rate of emergence of resistant variants is explained on a genetic basis on the theory that the combined drugs should select doubly resistant mutants that arise with a frequency determined by the product of the single mutation rates.[7] The exceptions are also based on other genetic principles that explain why multiple chemotherapy is not always helpful or may be only partially effective.[7] Combinations of antibiotics have been widely used clinically for infections other than tuberculosis chiefly for their additive or possibly synergistic effects and particularly in staphylococcal infections. There are as yet no reports of controlled studies from which the effect of such antibiotics on emergence of resistance can be evaluated.

Summary and Conclusions

An attempt has been made in this review to gather some of the available evidence for changes in resistance of bacteria resulting from administration of antibiotics and for the significance of those changes. The data concern chiefly the uses of antimicrobial agents for the therapy and prophylaxis of disease in human beings and for their growth-promoting effects in animals.

The data in human subjects relate both to changes in the susceptibility of certain originally sensitive pathogens and to changes in the microflora within the original host, and also concern the dissemination of resistant organisms during widespread usage.

Differences in susceptibility of streptococci appear to be related to particular species or types; this was clearly demonstrated for *Streptococcus pyogenes*, Types 17 and 19, which were resistant to sulfadiazine and accounted for epidemics during widespread use of sulfonamide prophylaxis. There was no evidence for resistance acquired either to sulfonamides or to any antibiotics in originally sensitive strains of *Str. pyogenes*. In the *Str. viridans* group and among enterococci there has been no change in the range of resistance even during prolonged treatment or prophylaxis with antibiotics, although the proportion of strains in the less susceptible end of the normal range may increase. Resistant strains developing in originally susceptible ones have been remarkably infrequent except in cases of bacterial endocarditis treated with erythromycin.

Micrococcus aureus has been the most troublesome. Numerous studies in hospitals and in other groups have indicated a marked increase in the incidence and spread of pathogenic, penicillinase-producing and penicillin-resistant strains that have also become increasingly resistant to all antibiotics that have been extensively used. The evidence suggests, however, that only for erythromycin has the increase in resistance of originally sensitive strains within the original host during treatment been frequent. The spread of resistant strains of *M. aureus* constitutes an important health problem. The incidence of resistant strains of *M. aureus* to any antibiotic appears to be related to the frequency and intensity with which it is used.

Mycobacterium tuberculosis is probably the only other organism in which resistance developing within the original host can be frequently demonstrated. This has occurred with each of the 3 principal antituberculous drugs, streptomycin, para-aminosalicylic acid and isoniazid. The development of resistance has been delayed and depressed but not prevented by the use of combinations of effective agents in proper dosage regimens. Resistant strains in previously untreated patients are appearing; at present they do not constitute a serious problem but prolonged and extensive domiciliary and ambulatory treatment in chronic cases, with persistent organisms, may constitute a public-health hazard.

The evidence regarding *Neisseria gonorrhoeae* indicates that sulfonamide-sensitive strains were suppressed while sulfonamide-resistant strains increased in prevalence during the widespread use of these agents, with concomitant loss of effect from such therapy. There is no substantiated evidence of any increased resistance to penicillin or other antibiotics among strains of gonococci in spite of the extensive use of these agents. Penicillin-resistant or sulfonamide-resistant strains of *N. meningitidis* likewise have not been encountered.

Strains of salmonella or of brucella have, with rare exception, not been noted to increase in resistance during prolonged treatment with any antibiotic including streptomycin.

Changes in flora of the urinary tracts of patients with chronic and complicated infections, with replacement of sensitive by resistant species, have followed

treatment with various antimicrobial agents. Only during treatment with streptomycin, however, have originally sensitive strains been frequently observed to acquire high degrees of resistance.

In the respiratory tract, also, the continued use of various antibiotics, either in large doses therapeutically or in smaller doses prophylactically, has resulted in the substitution of a flora resistant to the antimicrobial agents that are used. Small doses of penicillin, as used in the prophylaxis of streptococcal infections or when incorporated in dentifrices, have not significantly changed the flora or the range of susceptibility of the usual organisms encountered, although the proportion of strains in the less susceptible part of the normal range have increased at the expense of the less susceptible ones. When broad-spectrum or multiple antibiotics are used, a more resistant type of flora, including proteus, pseudomonas, resistant staphylococci and fungi, may emerge and may result in superinfections with such organisms.

In the intestinal flora of human beings, studies have been made during and after the preoperative preparation of patients for surgery of the bowel, using large doses of poorly absorbed sulfonamides or antibiotics, or combinations of both, coupled with mechanical cleansing and purging. These procedures have resulted in various degrees of lowering of the total aerobic counts, particularly the coliform organisms. This, however, has been temporary, and the total counts have returned to the original or higher levels in a few days even during continued administration of the antimicrobials. The resulting flora of the bowel is then resistant to the agents used, and pathogenic strains may become established, either in the bowel or elsewhere. Proteus, pseudomonas, aerobacter, *M. aureus* and various yeasts and fungi may emerge. Some of these, particularly *M. aureus,* have been responsible for serious disease.

The data in animals relate primarily to changes in the microflora of the intestinal tract during antibiotic supplementation of the feed. Although much smaller doses are involved, when compared with those used in human subjects, their use is accompanied by varying changes in the intestinal flora, depending on many factors, such as the different animals employed and the diets and antibiotics studied. The total bacterial counts, however, are generally not reduced, except temporarily during the first few days, and may then frequently be increased above the levels found in control animals. The species that persist and increase are predominantly resistant to the antibiotics being fed. The residual flora, however, appears to have a favorable effect on the nutrition of the animals. In contrast to the human experience, disease-producing strains have not been found to emerge among the types of animals that are raised primarily for market on antibiotic-supplemented feeds. Pathogenic organisms, however, have been observed to become prominent and apparently injurious in mice treated orally with streptomycin and in guinea pigs fed chlortetracycline, but larger amounts of these antibiotics had been used as compared with those added to feeds for growth-promoting effects.

The literature dealing with some of the biologic and biochemical properties of organisms made resistant in vitro that distinguish them from their parent sensitive strains has been reviewed. These differences vary with the species and with the antibiotic, and some appear to be more permanent than others; in many, however, the sensitive and resistant strains are indistinguishable, particularly after they have been subcultured without the relevant antibiotic. Only in *M. aureus* isolated from infectious lesions have penicillin-resistant strains been found to produce a specific penicillin-inactivating substance that distinguishes them from other resistant strains that were derived from originally sensitive ones by subcultures in penicillin in vitro.

Crossresistance between antibiotics has been most clearly and most regularly demonstrated in those that have closely related chemical structures, but there are exceptions in which such structural relations are not evident. Increases in sensitivity to heterologous agents may accompany the development of increased resistance resulting from repeated subcultures in some antibiotics.

The use of combinations of antibacterial substances to delay and depress the emergence of resistance in vitro has been demonstrated in various organisms and with a number of antimicrobial agents. Only for *Myco. tuberculosis,* however, has this been clearly demonstrated to occur in vivo during prolonged therapy.

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MEDICAL INTELLIGENCE

ACUTE SUPPURATIVE PAROTITIS*

Report of Two Cases

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ACUTE suppurative parotitis is no longer commonly encountered in surgical practice. Gustafson[1] found 5 cases in a three-year period (1947-1950) at the University Hospitals, University of Michigan. The opportunity to observe and treat 2 cases within a year in two widely separated hospitals has prompted this report.

CASE REPORTS

CASE 1. On March 26, 1954, a 38-year-old man in Walter Reed Army Hospital underwent pancreaticoduodenal resection for carcinoma of the ampulla of Vater. Oxytetracycline was given for prophylaxis against postoperative infection. On the 5th postoperative day moderate serous drainage from a lateral stab drain wound was noted, increasing as the diet was liberalized and excoriating the surrounding skin. Suction apparatus at the drainage site was installed, and the patient was given methantheline (Banthine) and less frequent feedings. The condition of the skin improved, and, although the drainage gradually decreased in amount it became thick and purulent. Cultures yielded hemolytic *Staphylococcus aureus,* alpha-hemolytic streptococci and *Aerobacter aerogenes.* The staphylococci and the *A. aerogenes* were resistant to the tetracyclines and streptomycin but sensitive to chloramphenicol. The staphylococci and streptococci were penicillin resistant but erythromycin sensitive. On the 25th postoperative day severe abdominal distress with nausea but no vomiting developed. Serum amylase determinations revealed no elevations. Serum sodium and blood sugar levels were not remarkable. The white-cell counts varied between 38,000 and 18,000, and the temperature between 100 and 102°F. There was no evidence of pleural effusion, and excretory urograms were normal. Gastric suction and intravenous infusions of fluids afforded relief of symptoms, and, after 3 days, a liquid diet was tolerated.

On the 29th postoperative day parotitis developed on the right, followed by involvement on the left 24 hours later. The patient could barely open his mouth. A small nasogastric feeding tube was inserted, through which he was given erythromycin, 400 mg., every 6 hours, which was continued for the next 5 days. At the same time he received a course of 9 x-ray treatments amounting to 500 r to the right and 400 r to the left parotid gland. Radiation was well tolerated. Subjective improvement was notable after 2 days of these treatments, and by the 5th day the patient was afebrile. The parotid swelling and induration disappeared. Fluctuation did not occur, and no cultures were ever obtained. Coincidentally, drainage from the abdominal wound ceased. The subsequent course was uneventful.

CASE 2. A 23-year-old man was admitted to Tripler Army Hospital for treatment of an areolar abscess of the right breast that had appeared 5 days earlier. Tetracycline by mouth was given, and the abscess, now pointing, was drained. Cultures grew coagulase-positive *Staph. aureus,* sensitive only to bacitracin, chloramphenicol and erythromycin. By the time this report was read the patient had been given 8 gm. of tetracycline over a 4-day period, drainage had ceased, evidence of infection had all but disappeared, and he was discharged. He stated that about 2 days later he noted pain in the left temporomandibular area, which increased in severity. After another 2 days he consulted a physician, who diagnosed the condition as mumps, and prescribed aspirin and codeine and gave daily injections of cortisone (amount unknown). Over the next 5 days the condition worsened, and the swelling and pain became bilateral. Purulent discharge developed from the left ear. He was admitted to the hospital on March 8, 10 days after the onset of symptoms. He was seen in consultation 2 days later, when a diagnosis of bilateral acute suppurative parotitis was made, on the basis of the local findings of swollen, hot, fluctuant and indurated tender masses over both parotid areas (the left more than the right) and the presence of purulent discharge in both ear canals. There was so much trismus that he could open the mouth for a distance of only 1 cm. There was no orchitis.

The temperature was 102°F. The white-cell count was 37,000, with 88 per cent neutrophils. Aspiration through a 15-gauge needle yielded 25 cc. of pus from the left, and 5 cc. of pus from the right parotid gland. On the basis that the prior mammary-gland infection was due to penicillin-resistant and tetracycline-resistant staphylococci, chloramphenicol therapy was begun, in a dosage of 0.5 gm. every 6 hours, together with a liquid dental diet. In addition, after each aspiration, chloramphenicol (0.5 gm. dissolved in 50 per cent solution of N; N-Dimethylacetanide) was instilled into each side in a dosage of 125 or 150 mg. Aspirations from the left parotid gland yielded 25, 15, 35, 10 and 5 cc. on the next succeeding days, with an average of 6 cc. each day from the right parotid gland. Rapid symptomatic improvement followed, and the temperature was within normal limits after 48 hours of therapy. The white-cell count was 19,300 3 days later, falling to 7500 in another 6 days. He tolerated a soft diet on the 6th day of treatment and was advanced to a regular diet 4 days later. Chloramphenicol by mouth was discontinued on the 15th day. No untoward reactions were noted.

Blood cultures yielded no growth. Cultures of the aspirates revealed heavy growth of hemolytic coagulase-positive *Staph. aureus,* resistant to penicillin and the tetracyclines but sensitive to chloramphenicol and erythromycin. On the 5th day, after aspiration and withdrawal of the needle from the left parotid gland, some tissue presented in the needle hole and was extracted with a sterile hemostat. The mass measured 2.5 by 2.5 by 1.5 cm. Histologic examination showed almost completely necrotic fibroadipose tissue infiltrated with degenerating inflammatory cells and containing numerous colonies of micrococci; the outer edge of the section could barely be identified as parotid gland. On the following day a similar but smaller mass of necrotic

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tissue was removed through the needle hole from the right parotid gland. Thereafter, the aspirates became sanguinopurulent and then serosanguineous, and 3 successive cultures yielded no growth. Drainage from the ears had ceased by this time. Complete subsidence followed.

Discussion

These patients had in common prior staphylococcal infection, superimposed on a pancreatic fistula in Case 1 and on an areolar abscess in the right breast in Case 2. A tetracycline antibiotic was given adjunctively to both. The staphylococci from both lesions were found to be resistant in vitro to the tetracycline antibiotics. In Case 1 the parotitis responded to erythromycin and x-ray therapy, and abscess formation did not occur. Although no cultures were obtained from the parotid lesion it can be assumed that the infection was caused by the same tetracycline-resistant staphylococci harbored in the pancreatic fistula since the patient had been receiving oxytetracycline when the parotitis developed. The organisms recovered from the parotid glands in Case 2 had the same antibiotic-sensitivity spectrum as the staphylococci recovered from the lesion of the prior mastitis. Specific (chloramphenicol) therapy was not initiated until the lesion had extended through the fascial layers of the gland through the external meatuses and extensive tissue necrosis had occurred. Cultures were positive for staphylococci until one day after removal of sequestrated necrotic parotid tissue. Repeated aspirations followed by instillations of chloramphenicol prevented unsightly scars, possible salivary fistula and troublesome secondary infection. It is impossible to state whether local chloramphenicol therapy helped the infection resolve. Bender et al.[2-4] found that a high degree of antimicrobial activity could be demonstrated in the buccal mucosa an hour after a single intravenous injection of the different antibiotics that they studied, and that this activity continued to be demonstrated for six hours or longer.

Whereas embolic infection of the parotid gland may occur, most commonly the infection ascends from the oropharynx via Stensen's duct. Jackson et al.[5] noted in patients treated with oxytetracycline for pneumonia that staphylococci rapidly and frequently emerged in the sputum and that almost all of them were highly resistant to this antibiotic. Assuming that a similar conversion of oral flora attended oxytetracycline therapy in the 2 cases reported above, infection via Stensen's duct can be postulated.

Acute secondary parotitis is uncommon, and when it does occur, *Staph. aureus* is the organism most frequently found.[1,6] In the light of increasing numbers of staphylococcal infections resistant to the commonly used antibiotics being encountered in hospitals,[7] specific therapy with chloramphenicol or erythromycin for suppurative parotitis seems warranted. Choice of therapy should be supported by bacteriologic studies whenever possible.

Summary

Two cases of bilateral acute secondary parotitis are reported. Early treatment with erythromycin and irradiation culminated in resolution of the infection in 1 case before the formation of abscesses. In the other case, treated late, massive destruction of the gland had already occurred. Resolution followed daily aspirations and chloramphenicol therapy.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41491

PRESENTATION OF CASE

First admission. A thirty-eight-year-old woman had a radical mastectomy for an undifferentiated carcinoma of the right breast that had metastasized to the axillary lymph nodes. X-ray examination of the chest showed an area of calcification in the apex of the right lung. A blood Hinton test was negative.

Second admission (eighteen years later). Postoperatively, the patient received 1600 r to the pelvis for sterilization and 3300 r to the right portion of the chest and axilla. On periodic visits to the tumor clinic over the next eighteen years she was found to be essentially well. A roentgenogram of the chest five years before admission showed a slightly mottled area of increased density with small flecks of calcification in the right apex. There was also a slight strandlike increase in density in the anterior segment of the right upper lobe suggesting postirradiation pneumonitis. A sputum examination done outside the hospital in the year before admission was reported as being positive for acid-fast bacilli. Three months before admission the patient noted the onset of intermittent right parietal and occipital headaches occasionally associated with "flashing lights." The headaches were made worse by coughing and sneezing and increased progressively in severity. Three weeks before admission she began to drop things. Others noticed that she began to stagger while walking. Two days before entry, she was unable to dress herself upon arising and had to call a neighbor for assistance. From that time to the time of admission her attention span was brief, and she was unable to do anything involving the use of the left hand.

Physical examination revealed absence of the right breast and pigmentation and telangiectasia of the wall of the right upper portion of the chest. No lymph nodes were palpable. The aortic second sound was greater than the pulmonic. There were no murmurs or cardiac enlargement. There was dullness over the right posterior portion of the chest near the apex. No rales were heard. There was a right-dorsal, left-lumbar scoliosis. The liver and spleen were not felt. The patient was alert, but was unable to concentrate on simple tasks. With simultaneous stimuli there was attention hemianopsia on the left. There was no papilledema or limitation of extraocular movements. The corneal reflex was questionably less active on the left. Cranial nerves were otherwise intact. Motor examination showed impairment of skilled movements on the left. Sensory examination disclosed decreased perception of vibration and position sense over the entire left half of the body. Simultaneous pin and touch stimuli on both sides of the body disclosed extinction of stimulus on the left side. Reflexes were equal and active, with an equivocal plantar response on the left and a flexor response on the right.

The temperature was 99°F., the pulse 80, and the respirations 16. The blood pressure was 120 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 11.8 gm. per 100 cc. and a white-cell count of 10,900, with 53 per cent neutrophils, 40 per cent lymphocytes, 3 per cent monocytes and 3 per cent eosinophils. The fasting blood sugar was 117 mg., the nonprotein nitrogen 28 mg., the protein 6.7 gm., with an albumin globulin ratio of 2.3, the cholesterol 217 mg., the calcium 9.2 mg., and the phosphorus 3.8 mg. per 100 cc. The prothrombin time was 16 seconds (normal, 13 seconds). An electrocardiogram appeared to be within normal limits. A skull film and metastatic series were normal. An x-ray film of the chest showed no appreciable change from the film taken five years previously. Acid-fast smears of the sputum were negative. Lumbar puncture revealed an initial cerebrospinal-fluid pressure equivalent to 142 mm. and a final pressure equivalent to 68 mm. of water. The fluid was clear and colorless and free of cells. The protein was 47 mg. per 100 cc., the gold-sol curve 0111210000, and the chloride 130 milliequiv. per liter. An electroencephalogram revealed a doubtful abnormality on the left side and a definite abnormality on the right, with occasional slow waves in all right temporal and parietal leads. A radioactive-arsenic scan of the brain was suggestive of a concentration in the left posterior temporal region and in the right parieto-occipital region.

The patient's illness stabilized, and she was discharged on the eighth hospital day to be followed in the Out Patient Department.

Final admission (two months later). After discharge the patient initially showed considerable improvement in co-ordination of movements and was able to do most of her housework. Two weeks before admission she complained of persistent left-sided headaches and a cough productive of blood-flecked sputum. The neurologic examination in the Out Patient Department was now negative, however. Two days

before entry, on arising, she was unable to support herself, showing primarily left-sided weakness. She was also confused.

The general physical examination was the same as on the previous admission except for the presence of a snapping aortic second sound and a Grade 1, rough, late diastolic murmur in the aortic area. Neurologic examination revealed a confused, drowsy woman. There was left-sided homonymous hemianopsia. There was weakness in the distribution of the left fifth and seventh cranial nerves, and the tongue deviated slightly to the left. Co-ordinated movements were poor in the left arm; however, the arm muscles appeared strong. The left leg was weak. There was a sensory deficit of the left half of the body. The left knee jerk was hyperactive; both ankle jerks were equivocal, and plantar responses flexor.

FIGURE 1. *Anteroposterior View of the Chest, Showing a Large Zone of Increased Density within the Right Upper Lobe Having Poorly Defined Peripheral Margins.*

The temperature was 99.8°F., the pulse 100, and the respirations 24. The blood pressure was 125 systolic, 60 diastolic.

Urinalysis showed a + test for albumin and 2 red cells and occasional white cells per high-power field in the sediment. Examination of the blood revealed a hemoglobin of 11.8 gm. per 100 cc. and a white-cell count of 14,800, with 51 per cent neutrophils, 16 per cent band forms, 22 per cent lymphocytes, 9 per cent monocytes and 2 per cent eosinophils. The prothrombin time was 14.5 seconds (normal, 13 seconds). The sedimentation rate was 20 mm. in one hour. An electrocardiogram showed a sinus tachycardia of 106 and transition complexes in all precordial leads. A roentgenogram of the chest demonstrated that the area of density noted before had increased considerably since the last observation and that there was extensive calcification of the ascending aorta (Fig. 1).

On the second hospital day the patient was given 900 mg. of Tromexan and 200 mg. of Dicumarol. Lumbar puncture on the fourth day revealed a cerebrospinal-fluid pressure equivalent to 85 mm. of water and 24 fresh red cells, 4 mononuclear cells and 1 neutrophil per cubic millimeter of fluid. The Pandy test was + +, the total protein 44 mg. and the sugar 77 mg. per 100 cc., and the gold-sol curve 0001100000. Later in the same day the patient was found to have a complete left-sided flaccid paralysis. The prothrombin time was now less than 10 per cent. For two days she had been coughing up small amounts of bloody sputum. On the eighth day, a few minutes after she had appeared unchanged, she was found to be unresponsive, with Cheyne–Stokes respiration. She now had exaggeration of reflexes and an extensor plantar response on the left. Within hours right-sided facial weakness was apparent, and there was an extensor plantar response on the right. The prothrombin time was 18 per cent. On the ninth day a lumbar puncture showed an initial cerebrospinal-fluid pressure equivalent to 110 mm. of water and xanthochromic fluid, with 850 fresh red cells per cubic millimeter in the third specimen. The Pandy test was + +. On the eleventh day the neurologic status was unchanged; however, the temperature was now 101.5°F., and the white-cell count 33,700. On the next day the aortic diastolic murmur was reported to have changed overnight from Grade 1 to Grade 3. On the thirteenth hospital day the temperature was 104°F. There were occasional clonic convulsions of the left arm and leg. Urine culture showed no growth. Achromycin was started. The patient died on the fourteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. ALFRED KRANES*: We are confronted with a patient having disturbances of three organs: the brain, the lungs and the heart. It is my job to try to elucidate what these abnormalities were and to determine whether they may have been related. In the background is the shadow of undifferentiated carcinoma of the breast with axillary metastases, removed eighteen years previously. Of primary interest are the cerebral symptoms, for which she entered the hospital and which eventually caused her death. I shall not try to localize this lesion or lesions precisely because I do not feel competent to do it, and because I am not sure that an accurate localization would be helpful in determining the underlying disease. There are three main possibilities — that the cerebral lesions were neoplastic, vascular or infectious. I was at first tempted to leave out of consideration an infectious etiology, but the fact that tubercle bacilli had been found in the sputum during the preceding year made me wonder whether the cerebral lesion or lesions may have been tuberculous in origin. However, further

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consideration makes that seem so improbable that I shall not discuss it further.

This brings me to a consideration of neoplasm versus vascular disease. The onset suggests neoplasm; it was gradual, starting with a headache and then with slowly increasing disability of the arm and the leg. In support of that is the radioactive-arsenic scan indicating lesions on both sides of the brain. Except for the onset the illness was more in keeping with a vascular origin. Although the illness began gradually, two days before she was admitted to the hospital there seems to have been a sudden increase in the symptoms to the point where she was unable to dress herself and had to call on a neighbor for assistance. That seems to me to indicate a sudden change at that point. Furthermore, it is of interest that a woman who was unable to dress herself and had to call for assistance when examined two days later in the hospital exhibited only some sensory loss on the left side and some inco-ordination in the movement of the left arm. This suggests that considerable improvement had taken place in the interval, and that is borne out by the fact that her symptoms cleared. So although the onset was gradual there was a sudden increase in the symptoms followed by a rapid improvement. This suggests a vascular cause. Certainly, the second episode, coming on abruptly and producing almost complete left-sided hemiplegia and hemianesthesia, with a left-sided homonymous hemianopsia, is even more suggestive of an occlusion of the right middle cerebral artery. I assume that those taking care of her had the same opinion because she was given anticoagulant therapy.

It is implied that the subsequent worsening of her condition may have been the result of the anticoagulant therapy because soon thereafter blood appeared in the spinal fluid and her condition grew worse. Whether the cerebral bleeding occurred because of the anticoagulant or whether it was the result of a cerebral infarction cannot be decided on the evidence available. There is some indication that the cerebral lesions may have been bilateral, as shown by the right-sided facial weakness terminally as well as the extensor plantar reflex on the right. On the whole it seems to me that the evidence favors multiple cerebrovascular accidents rather than tumor.

Pulmonary disease is occasionally associated with cerebral metastases, either of infectious or of neoplastic origin. I wonder what help I can get from the x-ray films. We are told that five years before the second admission this lesion was first noted, although nothing was said about whether any films had been taken during the previous thirteen years, after her operation.

DR. JOSEPH HANELIN: The first films that I have were taken thirteen years after operation.

DR. KRANES: So that the lesion described five years before the second admission may have been present for many years before that.

DR. BENJAMIN CASTLEMAN: Films of the chest taken two years after operation for carcinoma of the breast were said to give no evidence of metastases.

DR. HANELIN: It may have been present for some time; however, the changes initially observed are certainly not very striking. There are irregular calcifications at the apex of the lung and strands of density, which radiate from the superior aspect of the right-lung root into the upper portion of the lung. The calcified areas suggest old tuberculous lesions; the dense strands may have resulted from previous irradiation and probably represent fibrosis. Four years later, before the patient's admission to the outpatient department, the chest is rotated slightly differently, and any difference in the appearance of the lungs could be explained on that basis. It was pointed out in one of the last examinations that calcification was present in the ascending aorta. I think it is present five years before the second admission. This finding may occur not uncommonly with syphilitic aortitis. At the time of the final admission I think there had been a distinct change in the appearance of the density immediately adjacent to the upper portion of the right-lung root, which is larger and more homogeneous (Fig. 1).

DR. KRANES: Was there anything unusual about the heart except for the calcified ascending aorta?

DR. HANELIN: The heart is only slightly enlarged at best. We can see the calcification in the ascending aorta somewhat better later on, and possibly the aorta has become more tortuous.

DR. EDWARD F. BLAND: Is there any word about pulsations? Can you separate the expanding area from the aorta?

DR. HANELIN: Actually I cannot separate it; it overlies the aorta. Perhaps you are thinking in terms of an aneurysm; it does not strike me as being typical of an aneurysm. I believe we are dealing primarily with disease in the lung parenchyma.

The other films are normal. A set of films of the knees, not discussed in the protocol, were taken twelve years before the second admission when she had a joint effusion and again two years before the second admission when considerable degenerative joint change had developed. I do not know whether this woman had syphilis or not. Although it is possible that some interference with normal kinetic sensibility provoked degenerative changes, the changes are not typical of a Charcot joint.

DR. KRANES: Syphilis certainly must be considered in view of the development of the aortic diastolic murmur. One Hinton test was reported negative eighteen years before, but no subsequent Hinton tests were mentioned; either they were not done or they were negative.

DR. BLAND: There were two spinal-fluid examinations, were there not?

DR. KRANES: Nothing was said about the Hinton test on either one of those.

DR. KRANES: To return to the lung lesion for a moment, unlike the lesions in the heart and the brain, this was of much longer duration. It had been present for a minimum of five years and was gradually increasing in size, whereas the other lesions had been present at the most for months, possibly for only several weeks. Therefore it seems reasonable to believe that this may have had no relation to the remainder of the picture. I am intrigued by the fact that within the year preceding admission, tubercle bacilli were found in the sputum. This raises some questions: Where were they found, and what was done about them? If nothing was done about them, why not?

DR. HANELIN: You mentioned the gradual increase in the lesion of the lung. The only increase that I see took place over a three-month span.

DR. KRANES: Returning to the question of possible tuberculosis, if tubercle bacilli were found, what were the circumstances of their finding and was the patient given any treatment? Nothing was said, and I am a little puzzled.

DR. CASTLEMAN: Two sputum specimens examined at a health center were reported as being positive for tubercle bacilli.

DR. KRANES: Two sputums were positive?

DR. CASTLEMAN: Because of that she was referred to the pulmonary clinic.

DR. GEROLD SCHIEBLER: She never entered the pulmonary clinic.

DR. KRANES: It seems to me that only two possibilities need to be taken very seriously: one is tumor, either primary or metastatic, and the other is chronic infection, probably tuberculosis. It would be unusual for a metastasis from an undifferentiated carcinoma of the breast not to have shown more growth in five years than is evident in these films. The same reasoning should hold true of a primary bronchogenic carcinoma. Furthermore, this does not look like tumor. Do you agree with that, Dr. Hanelin?

DR. HANELIN: It certainly suggests infection, unless there were a mass in a segmental bronchus with peripheral atelectasis and pneumonitis.

DR. KRANES: It probably did represent pulmonary tuberculosis. It would have been of interest on either one of the admissions to have examined the sputum cytologically for tumor cells.

About the heart, I am told that an aortic diastolic murmur, rather rough in character, appeared within a two-month period and seemed to be increasing in intensity throughout the final days in the hospital. There was no evidence of any pre-existing heart disease — no evidence of any congestive heart failure or change in the size or configuration of the heart. From the information given I should judge that the electrocardiogram was normal. Do you agree with that, Dr. Bland?

DR. BLAND: This sounded more dramatic to me. One night the murmur was faint — Grade 1; the next day it apparently was much more impressive — Grade 3. One does not usually confuse a Grade 3 murmur with anything else.

DR. OSCAR E. STAROBIN: The description of the pain and murmurs is probably due to the fact that the person who wrote the protocol was not entirely familiar with the clinical course. Actually, different observers heard the murmur at various intensities during the same day. One person called it Grade 1, and the other Grade 3.

DR. KRANES: So that this observation may have represented a difference in observers rather than a difference in the intensity of the murmur. In any event there seems to be little question that this murmur had not been heard before and that it was a new development.

How can one fit all these pieces together? One wonders at first whether the whole chain of events might not best be explained on the basis of metastatic neoplasm either from the breast or from the bronchus. But for reasons that I have already indicated, I doubt if the lesions in the brain and the lung can be adequately explained on such a basis. Although carcinoma of the breast and bronchus are more likely to metastasize to the heart than any other type of tumor, they metastasize either to the pericardium or to the myocardium. It is very rare for tumor metastases to be found in the endocardium. The few that have been recorded were on either the mitral or tricuspid valve. I suppose that if I were to make an exhaustive search of the literature, I might find a tumor metastasis on the aortic valve, but it must be an extremely unusual occurrence. It is difficult for me to see how metastases in the myocardium could produce an aortic diastolic murmur.

For the explanation of the murmur I have to turn to some process within the heart itself. That would have to narrow down to rheumatic heart disease and bacterial endocarditis. As for rheumatic heart disease, there are occasional cases of mitral stenosis in which no typical mitral murmur is heard, but I am unwilling to offer such a diagnosis in this patient. Bacterial endocarditis, it seems to me, would explain all the findings, except those in the lung. The only trouble with it is that there is nothing to support it. The patient had no fever. Was there any fever on the first admission?

DR. SCHIEBLER: No.

DR. KRANES: She had no fever except terminally. She had none of the usual concomitants of this disease —no petechiae, no splenomegaly and no hematuria although there were 2 red cells per high-power field in one sample of urine. It should be mentioned that slight enlargement of the spleen, petechiae and so on are found only when one suspects the diagnosis of bacterial endocarditis and looks for them.

Since the frequency with which petechiae are found depends on one's index of suspicion, and since no blood cultures were taken on this patient, bacterial endocarditis was probably not very seriously con-

sidered, and these signs may not have been searched for. Another drawback is that the heart was previously normal and endocarditis is generally engrafted on diseased valves. Yet, in the last few years, more and more cases of endocarditis, particularly in middle aged and elderly people, with perfectly normal heart valves, have been described. I have seen several such patients myself, and have been unfortunate enough to have been asked to discuss 2, all of whom had normal heart valves. One did not even have the decency to have a cardiac murmur. One that I was asked to discuss had, in association, an asymptomatic carcinoma of the pancreas. This disease is referred to as marantic endocarditis, because it is often found in association with some debilitating disease, possibly tuberculosis in the case under discussion.

DR. BLAND: Would you discuss the normal sedimentation rate in relation to possible bacterial endocarditis?

DR. KRANES: What do you want me to say about it? I am unhappy about it, just as you are, and just as I am about the absence of other findings. Yet I can think of no other logical diagnosis that would explain this picture. I shall have to let it rest there.

DR. BLAND: Could you conceivably consider polyarteritis, still leaving out the lung lesion?

DR. KRANES: Yes; I think it is conceivable. I had thought it over, but because of the lack of time I did not discuss it. It seemed to me that endocarditis was a better explanation for the chain of events that were presented.

DR. JACOB LERMAN: What did you think the lung lesion was?

DR. KRANES: I thought it was probably tuberculosis, unrelated to the remainder of the picture.

DR. CASTLEMAN: What do you think it was, Dr Lerman?

DR. LERMAN: I think carcinoma of the lung is more likely than tuberculosis. Did not the x-ray film show calcification of the ascending aorta? That would raise the possibility of syphilitic aortitis.

DR. KRANES: I did not spend much time on that. The blood Hinton test was negative eighteen years previously, and that was the last one mentioned. Syphilitic aortitis is a possibility, but I do not think it is a good one.

DR. ALLAN L. FRIEDLICH: Is it possible that the murmur that was so variable, and had such a peculiar quality, was a friction rub?

DR. STAROBIN: We did not think so. There was no pulsus paradoxus, and there was nothing to suggest a friction rub.

The Service had many questions about the diagnosis. Blood cultures were done about six days before death before we started Achromycin therapy. Up to the time of death there was no growth in any of them. Three specimens of sputum were studied for tuberculosis by acid-fast staining and by inoculation into guinea pigs. The smears were negative for acid-fast bacilli. The guinea pigs had not yet been killed by the time of death but they were examined, and none of the lymph nodes were positive. The films of the chest taken immediately on admission showed no change from the previous films. Another point is that x-ray films taken ten and eleven years previously were interpreted as demonstrating postradiation pneumonitis, with strandlike density in the right upper lobe.

CLINICAL DIAGNOSES

Syphilitic aortitis.
Multiple cerebral emboli and infarctions.
?Bronchogenic carcinoma.

DR. ALFRED KRANES'S DIAGNOSES

Bacterial endocarditis, marantic.
Cerebral emboli, multiple, with infarction.
Tuberculosis of lung.

ANATOMICAL DIAGNOSES

Nonbacterial thrombotic endocarditis, aortic valve, with multiple emboli to and infarcts of brain, kidneys and heart, recent.
Adenocarcinoma, Grade 3, right upper lobe, with metastases to regional lymph nodes.
(Carcinoma, right breast, with axillary metastases, eighteen years).

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy the lesion in the lung proved to be a large yellowish-white, necrotic tumor just under the pleura. The pleura overlying it was fibrotic and thick, indicating that it had been present for a long time. Microscopical examination revealed a well differentiated adenocarcinoma of the type that we occasionally see associated with long-standing fibrosis. A number associated with tuberculosis, for example, have been reported. There was no evidence of active tuberculosis. A few small regional lymph nodes were involved with the carcinoma. We reviewed the slides of the old carcinoma of the breast and noted that its appearance was not very much like that of the new tumor. Although at first I thought that the pulmonary tumor conceivably was a metastasis, after studying it and having others study it, we agreed that it was probably a new tumor. It was well differentiated, with good gland formation and secretions in the cells. We found no evidence of carcinoma anywhere else in the body.

The heart was normal in size and gave no evidence of coronary-artery disease or pericarditis. All the valves except the aortic were normal. There was endocarditis along the line of closure of the aortic valve. It was granular, although the granules were not large, and gross inspection was consistent with a

bacterial endocarditis. There was no perforation of any of the cusps, and the granulations could be rubbed off fairly easily, although a little attachment still remained. The aorta above it showed a fair amount of sclerosis, with some calcification. From the gross appearance I believed that this was syphilitic aortitis although there was no separation of the cusps at the commissures to allow for the free regurgitation that one sees with a syphilitic aortitis. Microscopically, however, there was no evidence of syphilis.

DR. BLAND: Was that sclerosis restricted to the root of the aorta?

DR. CASTLEMAN: No; it involved the whole aorta. We made many sections of the valves and of the entire heart looking for organisms in the thrombi, but we could not find any. I think, Dr. Kranes, that this fits in with the condition that you suggested, the marantic endocarditis that is seen in patients with carcinoma or debilitating diseases—the nonbacterial, thrombotic form of endocarditis. Usually, this does

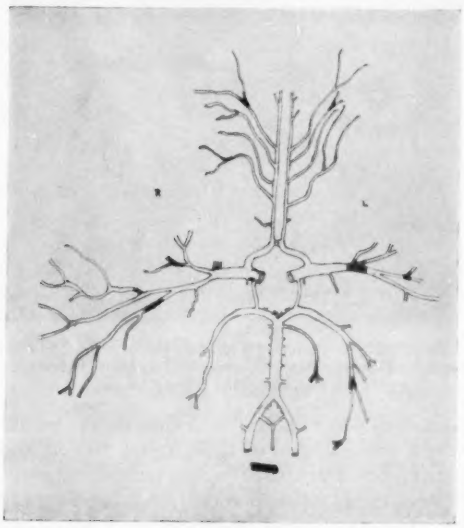

FIGURE 2.

not give rise to emboli, but it may and in this case it did.

DR. KRANES: The patients I have been asked to discuss all had emboli.

DR. CASTLEMAN: It was difficult to find evidence that these had been present for a long time; they all looked recent, but in some of the sections we did find evidence of organization at the base, suggesting that this had been present for a long time.

There were emboli to the kidneys and to the myocardium, producing tiny miliary infarcts. There were numerous emboli to the brain, which Dr. Hakim will show you.

DR. BLAND: Because there was no infection, the sedimentation rate was normal.

DR. CASTLEMAN: This was not subacute bacterial endocarditis; at least we could find no organisms. They were platelet thrombi for the most part.

DR. SALOMON HAKIM: The brain appeared grossly softened and friable in various places, the right hemisphere being the most affected. There was marked temporal coning of the left side. The vessels of the circle of Willis were almost free from atherosclerosis.

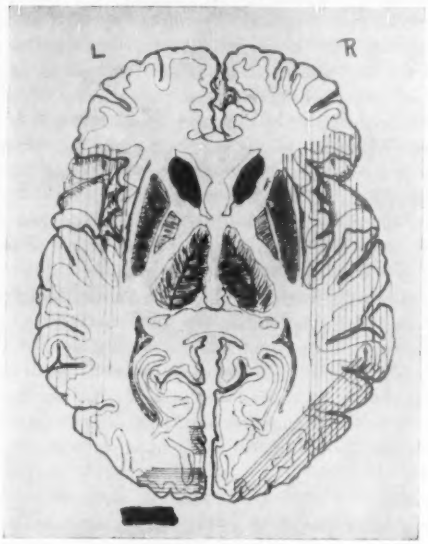

FIGURE 3.

The dissection of its branches disclosed multiple emboli bilaterally (Fig. 2). The left posterior cerebral artery contained the oldest embolus. One of the posterior branches of the right middle cerebral artery contained the next oldest embolus, and the left middle cerebral artery and both anterior cerebral arteries showed more recent emboli of about the same age. The microscopical sections of the occluded vessels demonstrated their lumens to be filled with the same material found in the aortic valve. The horizontal sections of the brain showed zones of partially ischemic and slightly hemorrhagic infarct, which could be the explanation for the blood found in the cerebrospinal fluid. A schematic drawing (Fig. 3) of a horizontal section of the brain through the basal ganglions shows the infarcted areas. The density of the linear shadows signifies the approximate ages of the infarcts and corresponds to the ages of the emboli.

DR. CASTLEMAN: Dr. Adams, have you a comment?

DR. RAYMOND D. ADAMS: Cases such as the one under discussion have radically altered our opinion concerning the neurologic complications of so-called marantic endocarditis. For many years we have observed that these aseptic thrombotic vegetations on the heart valves were not merely an unimportant terminal event but could be a not too infrequent source of

brain embolism. Moreover, it appears that there is some relation between these vegetations in the heart and carcinomatosis. We have observed several cases, all verified at autopsy, in which an embolic occlusion of a brain artery was the first symptom of a carcinoma, or it had given rise to apoplexy in a patient known to have a carcinoma in one or several organs. The carcinoma in these cases has been in any one of several sites,—stomach, ovary, lung,—and the emboli may recur over a period of months. As with all types of embolism, the brain is frequently involved and is usually symptomatic. The clinical diagnosis of this unusual type of cerebrovascular disease depends usually on evidence of the carcinoma and signs of embolism. Apoplexy in the carcinomatous patient more often proves to be due to aseptic embolism than to tumor emboli or cerebral metastases.

The basic disorder in this condition has not been determined. These emboli and vascular thrombi are composed of masses of fibrin and platelets. There are no tumor cells in them. The same thrombotic tendency may be responsible for the common phlebothromboses of carcinoma.

Finally, it should be pointed out that this type of "endocarditis" may also occur in serious debilitating diseases other than carcinomatosis—hence the term "marantic," which is still retained in some circles.

CASE 41492

Presentation of Case

A fifty-year-old carpenter entered the hospital because of upper abdominal pain.

Two months before admission the patient first noted pain deep in the midepigastrium that radiated to the back and persisted for about a week. It was not related to food or time of day, and it was not relieved by rest or exacerbated by activity. No fatty-food intolerance was noted although he had refrained from eating fatty foods in recent years. An upper gastrointestinal series was normal. X-ray films at this time showed slight degenerative disease in the joints of the thoracic and lumbar spine. Five weeks before entry the pain recurred and persisted. Since the onset of his illness he had had anorexia and noted a 15-pound weight loss. Five days before admission he vomited a small quantity of bile-colored fluid and later had several similar episodes, with small, bright-red flecks of blood noted in the vomitus. Bowel movements were regular, and the stools were normal in color except for some spotting with blood. There was no history of jaundice or dark-colored urine. In the past he had been a heavy drinker of alcohol but denied consumption of any alcoholic beverages in the previous three years.

Physical examination revealed a thin man in no acute distress. Breath sounds were decreased, and there was slight dullness throughout the left side of the chest. The heart was normal. There was moderate guarding of the abdomen but no significant tenderness. The liver and spleen were not palpable. The upper border of liver dullness was percussed in the fifth right intercostal space. Rectal examination showed external hemorrhoids.

The temperature was 98.8°F., the pulse 84, and the respirations 16. The blood pressure was 106 systolic, 65 diastolic.

Figure 1. *Right Anterior Oblique View of the Stomach, Showing a Pressure Deformity on the Posterior Aspect of the Upper Portion of the Body (Arrows).*

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 13.9 gm. per 100 cc. and a white-cell count of 10,300, with a normal differential. The erythrocyte sedimentation rate was 31 mm. per hour. The total serum protein was 7.7 gm., the albumin 5.1 gm., the globulin 2.6 gm., the serum calcium 9.8 mg., the phosphorus 3.9 mg., and the alkaline phosphatase 5.3 units per 100 cc. The serum amylase was 20 Russell units per 100 cc., and the lipase 0.66 cc. Three stool specimens gave negative guaiac tests. A glucose tolerance test was normal. Gastric analysis showed no free acid before and 11 units of free acid after histamine. Cytologic examination of the stomach contents for tumor cells was negative. Cerebrospinal-fluid examination was negative except for a protein of 51 mg. per 100 cc. An upper gastrointestinal series showed an active duodenal ulcer measuring 1 cm. in greatest diameter. An intravenous pyelogram was normal except for a double pelvis and ureter on the right side.

The patient was placed on an ulcer regimen, but this failed to relieve the symptoms. X-ray studies on

the thirteenth hospital day were negative except for a questionable ulcer crater along the midportion of the lesser curvature of the stomach and moderate antral spasm. A subsequent upper gastrointestinal series on the next day showed no abnormalities (Fig. 1). On the twenty-first hospital day an operation was performed.

Differential Diagnosis

Dr. Leonard W. Cronkhite, Jr.*: This case well re-emphasizes the problem of diagnosis of pain of an obscure nature in the upper abdomen. The salient historical features are steady, boring pain of rather short duration, with radiation through to the back, considerable weight loss (15 pounds), anorexia and vomiting, in the absence of jaundice. Since the reports of the x-ray examinations are confusing and since it is important to decide whether the lesion was extrinsic to or intrinsic in the gastrointestinal tract, may I look at the films first? Four gastrointestinal series were done: the first and fourth were normal, the second showed a duodenal ulcer, and the third revealed a questionable ulcer on the lesser curvature.

Dr. Joseph Hanelin: The examinations of the upper gastrointestinal tract extend over a six-week period; the initial study was regarded as negative. When the patient came into the hospital, there was question of a duodenal ulcer, which I find difficult to be certain of from the films that we have. When he was re-examined there was no evidence of a duodenal ulcer, but there was suspicion of a gastric ulcer along the lesser curvature. Certainly, a projection of barium of this nature warrants a repeat study. Two days later there was no indication of either a duodenal or a gastric ulcer. If one looks at all the films there is one persistent finding that may be of importance — that is, the suggestion of extrinsic pressure on the posterior aspect of the body of the stomach. It may be slightly greater in the last examination than in the first (Fig. 1), but there is some suggestion of pressure deformity in all the films of that area. The other examinations are noncontributory.

Dr. Cronkhite: The physical findings in this case were not very helpful; none of the organs in the abdomen were palpable, nor were any masses felt. The prostate was not mentioned specifically, but the x-ray films of the thoracic and lumbar spine seem to point away from any difficulty with that organ. The results of the laboratory examinations were not very abnormal, but a few were borderline. The blood was normal except for the slight elevation of the white-cell count and an increased sedimentation rate. The alkaline phosphatase was slightly over the normal of 4.5 mg. per 100 cc. The amylase was 20 Russell units; the laboratory considers 8 to 18 units by the Russell method normal, but by experience we know that readings of 40 to 45 units can be completely ignored in some cases; there needs to be marked elevation to be of significance. The lipase was well within normal limits.

The problem in obscure abdominal pain of this nature is to decide whether the disease lies within the gastrointestinal tract or is extrinsic to it. Of those within the gastrointestinal tract, the presence or absence of ulcer eventually enters the debate. I cannot take the x-ray findings seriously since they were inconstant in their presence and location. Carcinoma of the stomach, with negative guaiac tests on the stool and a negative cytologic study, would have to be of the diffuse, infiltrating type in which the mucosal lining of the stomach was not tremendously involved. There is so little evidence on which to base a diagnosis of carcinoma of the stomach that I shall not consider it further. Other neoplastic lesions in the stomach that may be diffuse or infiltrating, such as malignant lymphoma and leiomyosarcoma, are probably worth mentioning. Again, I am hampered in making one of these diagnoses by lack of positive evidence that there was disease intrinsic to the stomach. Nor is there evidence of carcinoma of the ampulla or of the biliary tract because jaundice was not present.

Of the lesions that may lie extrinsic to the gastrointestinal tract I think the most likely is carcinoma of the pancreas. In the old literature on carcinoma of the pancreas jaundice is present as a very prominent finding, but whether the jaundice occurs early or late in the disease — or indeed occurs at all — depends somewhat on the location of the carcinoma. I have no reason to suspect that there was any difficulty around the head of the pancreas, but I find nothing in either the history or findings incompatible with carcinoma of the body or tail of the pancreas. Such a carcinoma is characterized by upper abdominal pain radiating to the back, quite profound weight loss and anorexia. In spite of the fact that no mass was palpated, I think that that is an excellent possibility.

Cyst of the pancreas is another possibility. The ordinary pancreatic cyst may grow to a tremendous size before it produces many symptoms and then is usually quite easily palpable. A very small proportion of pancreatic cysts will have malignant change and be called cystadenocarcinomas by the pathologists. The mechanism of weight loss with a benign pancreatic cyst is still obscure in cases in which there is no profound nausea and vomiting. To make a diagnosis of pancreatic cyst, one likes to have the history of preceding episodes of what could be called acute pancreatitis or a history of recurrent unexplained abdominal episodes. In this case the only suggestive point in the history is that the patient was at one time a heavy consumer of alcohol.

Other areas in this part of the abdomen can be involved in neoplastic disease and probably warrant mention. Occasionally, a patient will have a history similar to this and will have a neoplasm arising from

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the sympathetic chain; therefore, a neurogenic sarcoma should at least be considered. The only other organs in this area that might have been involved are the lymph nodes behind the stomach and along the vertebral bodies, and these could give rise to a malignant lymphoma.

I think that one has to make a diagnosis on the basis of statistical possibilities rather than on definite leads in the protocol. The diagnosis most likely is carcinoma of the pancreas, probably involving the body and tail, but the possibility of neurogenic sarcoma or of a diffuse, infiltrating neoplasm of the stomach is equally good. I do not see any need to consider diseases other than neoplasm since none of the characteristics of the more common inflammatory diseases or infections were present.

DR. BENJAMIN CASTLEMAN: Dr. Hanelin, would the x-ray picture fit with the diagnosis of carcinoma of the body and tail of the pancreas?

DR. HANELIN: It would be consistent with that and with any extrinsic lesion arising posterior to the stomach and of sufficient size to cause a pressure deformity. It would be unlikely to result from an intrinsic gastric lesion, although rare spindle-cell tumors of the stomach may have this appearance. I should not suspect an infiltrating lesion of the stomach in this case.

DR. RICHARD B. COHEN: Dr. Point, have you a comment?

DR. WARREN POINT: This case was quite a problem because there were so few objective signs. All the tests were negative except for the sedimentation rate and the amylase, which were borderline. We did analyze a stool for fat and muscle fibers because it has been stated that a large number of patients with carcinoma of the pancreas, even in the relatively early stage, will have excessive loss of fat and undigested muscle fibers because of obstruction of the pancreatic duct. That was one more negative test to confuse us. The picture the patient presented was that of a malignant tumor of the pancreas. He looked sick, he assumed the characteristic position: as time went on he felt better sitting up. We all realized that if this was indeed carcinoma of the pancreas, we had never effected a cure, but we had to know and the patient had to know what was going on because he was becoming intolerably miserable. With that diagnosis in mind, he was explored.

CLINICAL DIAGNOSIS

?Carcinoma of pancreas.

DR. LEONARD W. CRONKHITE, JR.'S, DIAGNOSIS

Carcinoma of body or tail of pancreas.

ANATOMICAL DIAGNOSIS

Carcinoma of body and tail of pancreas.

PATHOLOGICAL DISCUSSION

DR. COHEN: At the time of the exploratory operation a mass was felt in the region of the tail and body of the pancreas, which was adherent to the hilus of the spleen. A nodule was also felt in the posterior peritoneum close to the main mass. A biopsy of the nodule showed adenocarcinoma. A resection of the body and tail of the pancreas and the spleen was performed. The distal 5 cm. of the pancreas expanded abruptly into a mass, 4 or 5 cm. in diameter, which was adherent to and infiltrating into the spleen. Microscopically, the tumor was a very mature adenocarcinoma, epithelial components of which simulated very closely normal pancreatic ducts and acini. These were distributed in dense fibrous tissue. It is this maturity of structure, common in adenocarcinoma of the pancreas, and its tendency to stimulate fibrous-tissue reaction that often makes the differential diagnosis between adenocarcinoma and a chronic fibrosing pancreatitis a difficult one. This is particularly true in frozen-section diagnosis. The pathologist must often depend on the detection of mild degrees of cellular atypicality; particularly helpful when present is the invasion of tumor into perineural lymphatics.

Carcinoma of the body and tail comprise about 40 per cent of the carcinomas of the pancreas. As Dr. Point mentioned, the prognosis is particularly poor in these cases because the first symptoms are nonspecific and often result from extensions or metastases of the tumor. In this case at operation there were no signs of metastases other than a local peritoneal nodule.

Dr. Point, do you know how this man is getting along?

DR. POINT: The surgeons thought, on the basis of what was seen at operation, that they had removed all the tumor. Of course, no one was naïve enough to believe that the patient had much chance because of the poor record that carcinoma of the pancreas has. After operation he continued to have severe left-sided pain up and down the entire back, whereas before it had been located in the lumbar region. He spent two weeks at home; then because of the severe pain he came back to the hospital five weeks after the operation. At that time a nerve-root section was considered seriously. When the situation was put up to him, he elected not to have the operation and decided that he could live with his discomfort. To my knowledge he is still doing so. I have not heard in the last two weeks.

DR. H. L. HEYL: May I ask about the mechanism of the pain?

DR. COHEN: I suppose that there are multiple mechanisms of pain. I think one possibility that cannot be excluded is the presence of further metastases in and around the vertebral column and the spinal nerves. Infiltration of nerves and peritoneum by tumor probably contributes considerably to the pain in these cases.

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"GROUNDEDLY LEARNED"

Two of the major problems in medical education relate to its continued evolution as a technical, social and cultural discipline and to the very real present-day concern over its financial predicament. Late in August there appeared almost simultaneously the fourth annual report of the American Medical Education Foundation and the Educational Number of the *British Medical Journal*. Each cast some light on the problem with whose solution it was concerned.

According to the report of the American Medical Education Foundation, $1,824,269.15 was contributed in 1954 directly to the medical schools of the country by their alumni, and $1,181,928.63 was given through the agency of the Foundation. Both the sums donated and the numbers contributing have risen steadily during the four years since the Foundation's inception, so large reductions at least are being made in the estimated annual deficit of $10,000,000 sustained by the country's medical schools.

The *British Medical Journal* of August 27, 1955, in six of the ten articles constituting the body of its Educational Number, deals with the continuing education of the physician under the term "adult education." The implication is one not merely of maturity in point of years but of a scholarly type of cultural broadening and strengthening beyond the ordinary concept of what is presented in postgraduate courses. The latter, according to this thesis, connote a furtherance of practical, technical training — a laudable and indeed essential brush up in the newer methods of diagnosis and treatment but with no particular emphasis on contemplation or spiritual refreshment.

The contributors to the above-mentioned number of the *British Medical Journal*, writing in support of adult education as a reflective phenomenon, represent the consultant, the preclinical scientist, the academic clinical teacher and the general practitioner. Two of them, in fact, write from the point of view of the general practitioner, who still represents the backbone of British medicine. The term adult education is proposed and defended by that dean among British educators, Sir Richard Livingstone — who credits the idea with some two thousand years of practice — and emphasizes the contrast between intellectual development and a brush up in technic. "Thought without experience and experience without thought are barren. When the two are wedded, wisdom is born."

There are and for a long time have been two conflicting although overlapping schools of thought regarding the theory and the practice both of medical education and of the art itself. The one regards medical practice as a skilled technic, carried on by a guild under the name of a profession; the other considers it as a truly learned calling whose practitioners are or should be persons of scholarly attainment as well as of high technical training. Both types are normally represented in medicine although the average doctor

would probably prefer to think of himself as a broadly educated individual rather than as a technician, however skilled. Even by their own testimony British physicians are debited with a shortage of general education at the college level, for they start their training in medicine at a much earlier age than is now academically possible in the United States.

The Linacre Lecture on "The Integration of Medicine" by Sir Harold Himsworth, secretary of the Medical Research Council, published in the *British Medical Journal* of July 23, 1955, serves as what the learned editor of that scholarly journal calls a prolegomenon to the symposium that has just been discussed. Linacre, one is reminded, founded the Royal College of Physicians of London on the principle "that our profession should contain men who are not only deeply studied in physic but groundedly learned."

Linacre himself, outstandingly a "doctor afield," an early fellow of All Souls at Oxford, was instrumental in developing the study of Greek at that university. Attached at twenty-five to the embassy in Italy he commenced the study of medicine at Padua two years later and became in time both tutor and physician to the Prince of Wales. His greatest contribution to medicine, however, was not in its practice but in its organization and the establishment of standards of practice. At forty-nine he was ordained, as further evidence of his grounded learning.

"Professions," according to Himsworth, "arise in response to the recognition of a social need, and their continued existence is dependent on their success in satisfying the expectations raised by the state of the knowledge which they profess." With a vast increase in medical knowledge and the consequent need of specialization, increasing complications have developed, but the difficulties in practice and the extension of its services have not arisen from specialization, as the unthinking may believe, but from the failure of integration. The failure, and the need of its correction, was brought out at the First International Conference on Medical Education in 1953; the warning has been many times repeated, both before and since the conference took place.

RESISTANCE OF BACTERIA TO ANTIBIOTICS

In this and the two preceding issues of the *Journal* a long and heavily documented Medical Progress report on the problem of resistance of bacteria to antibiotics is presented. In spite of the monumental bibliographic appendage representing a contribution usually discouraged by the editors, it can hardly be said that the author exhausted even the part of the literature on the subject that appears in the English language. Rather sparse, also, are the references to papers in foreign languages, which, unfortunately, are usually difficult and often impossible to cover even by one who makes a serious effort to be thorough. The paucity of pertinent papers on the subject appearing in other languages is only partly responsible for this, because increasing numbers of workers in various parts of the world are becoming intensely interested in the problem, particularly since more and more countries are finding it possible either to purchase from outside or to produce within their own borders many of the useful antibiotics. The demand for their use has generally paralleled their availability under such circumstances.

The author of this review has particularly emphasized the distinction between the same, originally sensitive organisms that have acquired increased resistance within the original host during the course of administration of the antibiotic on the one hand and the changes in flora during similar exposure to the antibiotic, whereby sensitive strains and species are eliminated and resistant ones emerge, on the other. The distinction is highly pertinent, for, in the former, therapy or prophylaxis of the infection by the causative organisms against which the antibiotic is directed becomes invalidated, and if this occurs during the course of therapy before a cure has been accomplished, the treatment may not be successful. On the other hand, changes in flora during antibiotic administration need not be harmful; moreover, as pointed out in this review, it even appears to be useful in animals that are given small amounts of antibiotics as feed supplements.

In the therapy of human beings, and sometimes even during prophylaxis, the emerging resistant species may be pathogenic, or may acquire pathogenicity, either because of more favorable conditions of competition against other bacteria, through removal of "antagonistic species," or because of some special susceptibility of the host under the particular circumstances, or possibly because the numbers of these organisms increase so that they approach and surpass the minimum infective dose.

Of particular interest is the small number of species of bacteria in which the factor of increasing resistance of originally sensitive strains of the original causative organism of the disease results from therapy of the original infection. Resistance developing in *Mycobacterium tuberculosis* during treatment with antituberculous drugs, especially when used singly, is the best example, as well as the one most thoroughly documented. Even for *Micrococcus aureus,* this factor has not been shown to be the major or primary factor in the increasing number of resistant strains. Organisms (that is, staphylococci) from foci not readily subject to reinfection from other sources, as in unoperated cases of osteomyelitis, or in bacterial endocarditis, ordinarily do not exhibit increasing resistance in successive strains cultured from the blood; they usually retain their original susceptibility to the antibiotic used for therapy in the great majority of

cases. There are exceptions, of course, as pointed out in cases of bacterial endocarditis in which staphylococci and various streptococci have exhibited steadily increasing resistance to erythromycin during treatment with that agent.

The problem of antibiotic-resistant staphylococci, as pointed out in this review and by many other workers, is one of crossinfection or superinfection by antibiotic-resistant strains acquired in hospitals in almost all cases. The incidence of strains of staphylococci resistant to any single antibiotic or any group of antibiotics in any given hospital appears to be directly related to the intensity with which those antibiotics are used in that hospital, and is also associated with a similar incidence of carriers of such resistant strains among the staff and service personnel of that hospital. To be sure, the resistant staphylococci may have acquired their unusual degree of resistance as a result of earlier exposures to the antibiotics in question; this has been clearly demonstrated for erythromycin, and is probably also true of the tetracyclines and of streptomycin. Regarding penicillin resistance, however, this property appears to be a naturally occurring one, peculiar to certain strains and associated with the ability of such strains to produce the penicillin-inactivating enzyme, penicillinase. The development of steadily increasing resistance of staphylococci (and some other organisms) during treatment has been clearly demonstrated in patients receiving erythromycin. Organisms other than staphylococci and tubercle bacilli have been noted, of course, to become resistant to streptomycin during treatment with that antibiotic; this may occur either gradually or in a single large step.

The effect of bacterial resistance on the future of antibiotic therapy may depend, to some extent at least, on the recognition of the types of resistance so emphatically distinguished here. The emergence of resistance in pathogenic bacteria within the original host during treatment should call for certain measures, such as the use of antibiotics in proper combinations or switching from one effective agent to another until a cure is obtained. This aspect is well illustrated in the therapy of tuberculosis, and more recently in staphylococcal infections. Changes in flora, on the other hand, are perhaps best tackled by a search for highly specific antimicrobial agents that would affect only the individual pathogenic species (or perhaps related ones as well) and would still permit the common commensals to retain their usual interrelations. Alternatively, it may be possible to discover new antibiotics that would eradicate, or at least inhibit, species that have been emerging and spreading and have been the cause of antibiotic-resistant infections. The spread of resistant species also calls for the development of technics of prevention; such methods have, thus far, been either inadequate or not pursued with sufficient vigor.

The nosocomial aspect of antibiotic resistance, as illustrated by the spread of resistant staphylococci and by the increasing occurrence of such resistant species as proteus, pseudomonas, aerobacter and possibly candida, should not imply that the problem will necessarily remain one confined to hospitals. The increasing numbers of persons receiving hospital treatment who are discharged into the community and the large numbers of patients receiving antibiotics at home or on an ambulatory basis are certain to have their effects in the community and may constitute a public-health problem. Some evidence that this is possible was cited regarding staphylococci and tubercle bacilli in this review.

ASSOCIATION ON ALCOHOLISM

THE headquarters of the Massachusetts Medical Society served as the meeting ground, in October, when a group of physicians and professional workers interested in the treatment and prevention of alcoholism formed the Professional Association on Alcoholism — the first of its kind in the United States. At the time of its organization Dr. James I. Roberts, medical director of the New England Electric System and associate director of the New England Medical Center, was elected president of the new association. Dr. Robert Fleming, instructor in psychiatry at Harvard Medical School and director of the Alcoholic Clinic at the Peter Bent Brigham Hospital, was chosen vice president, and Dr. David Landau, instructor in psychiatry at Tufts University School of Medicine and medical director of the Boston Committee on Alcoholism, was elected secretary and treasurer.

The purposes of the Association, which was sponsored by the Boston Committee on Alcoholism, are to promote research on alcoholism and, presumably, to put on a national basis and co-ordinate the various efforts that are being made to combat this ubiquitous disease. Among its functions will be not necessarily the establishment of another foundation, but the solicitation from foundations already existing of funds for these most important medical and sociologic studies.

It is intended that the membership of the Association should be drawn from physicians, hospital administrators, nurses, sociologists, social workers and any others who might be interested in the problem.

PLASTIC-PECKING PIGEONS

THE effects of chlorpromazine and phenobarbital on the plastic-pecking propensities of pigeons at Harvard Medical School was reported in September at the fall meeting of the American Society for Pharmacology and Experimental Medicine, according to a release from the University News Office. The pigeons

under study were assigned to a set task consisting of pecking at a piece of plastic, the rate of pecking depending on whether a red or a blue light was percolating through the plastic piece. Under the ground rules established for the experiment the red light, contrary to usual procedures, was the signal for the pecking to commence, and a pause ensued between the red-light pecking and the blue-light pecking.

This was all very well under normal conditions, the industry of the pigeons being rewarded by the proffer of pabulum — presumably corn. With the pigeons under the influence of chlorpromazine, the so-called tranquilizing agent, a different pecking pattern prevailed, however. Although correct performance continued regardless of the color of the light, the pauses at the change of lights were protracted, the intervals between pecks were prolonged, and the particular pigeon, although normal in appearance, presented an apathetic personality.

Phenobarbital was responsible for a different pattern. When this drug was fed to the pigeons the pause preceding the pecking when the blue light was produced tended to disappear, the rate of pecking was retarded and "tended to be much more irregular and uneven than after chlorpromazine." These problems pertaining to the pecking of plastic by properly trained pigeons, and the methods of studying them, according to the investigators, "permit the behavior of animals to be controlled so effectively that it is possible to accurately predict what they would have done if they had not received a drug." It was not stated whether any of the pigeons were rendered aplastic by properties pertaining to either type of pill or by the nature of the plastic pecked.

We learn from a gentleman who left Trieste on the 10th ult., that the cholera had raged there most frightfully from the 28th of May last, but was fast disappearing . . . The American Consul, William A. Buffum, Esq., remained faithfully at his post during the whole season, notwithstanding the panic among the residents, and there has been some talk of presenting him a handsome testimonial.—N. Y. Commercial Adv.

Boston M. & S. J., *Dec. 13, 1855*

MASSACHUSETTS MEDICAL SOCIETY

SOLOMON R. KAGAN
1889-1955

In the death of Dr. Solomon R. Kagan on July 27, 1955, the Boston community, and particularly the medical profession, lost an unusual personality, a man tirelessly devoted for over half a century to Talmudic and medical lore.

Born in Russian Lithuania on December 15, 1889, and reared in a family of rabbis, he was ordained a rabbi at an early age. He had set his heart, however, on a career in medicine, and after years of the traditional hardship of the Eastern European Jewish student, he received his degree in medicine at Dorpat University in 1917. He then served as government physician and health officer for five years, during which he had the opportunity to study and to report on an epidemic of typhus fever.

In 1922 he came to the United States, settling first in Springfield and later in Boston, where he established a good practice in general medicine and physiotherapy, studying and reporting his clinical observations, serving on the staff of the Jewish Memorial Hospital and attaining an honorable place in the community. Ill-health, unfortunately, forced him to retire from practice in 1935.

Happily, he was able to continue with his literary activity, which by tradition and training had led him to studies in rabbinic literature and in the medical lore of the Bible and the Talmud. This in turn led him to research in the bypaths of medical history, bibliography and biography, particularly of Jewish physicians in America.

Dr. Kagan's inquiries and prolific writing widened his sphere of correspondence with outstanding men in this field, among them Max Neuberger, Humphrey Rolleston, Henri Baruk, James J. Walsh, Sussman Muntner, Henry Sigerist and Fielding H. Garrison. He held honorary membership in several historical organizations, including the Eugene Field Society and the Israel Association of the History of Medicine, and was treasurer of the American Physicians' Fellowship Committee of the Israel Medical Association.

He was associated in co-editorial work in the *Medical Leaves,* the *Hebrew Physician,* the Max Neuberger anniversary number of the *Medical Record,* the *Victor Robinson Memorial Volume* and the *Abraham Levinson Anniversary Volume.* In his 2 volumes on Fielding H. Garrison he made available the rich personal correspondence of this outstanding medical historian. In the several volumes and numerous papers on Jewish physicians, encyclopedic in scope, he left source material on many personalities who otherwise would have been doomed to oblivion. Through this work Dr. Kagan's name will also live on.

In the preface to his last volume, *Jewish Medicine,* published on the occasion of his sixtieth birthday, he evaluated the contribution of Jews to medicine in the spirit of Professor H. Haberling, who wrote in the preface to his work, *German Medicine,* as follows:

> When in the present study I write about "German Medicine" I do not wish to suggest that certain phases in the history of medicine were created by the Germans. Rather I picture medicine as a clock work in which the different wheels catch and turn each other to bring about the perfect movement. Each of the wheels represents a nation.

Dr. Kagan adopted the same attitude toward Jewish medicine:

> In the same spirit, I wish to make it clear that in my discussion of Jewish medicine I am presenting the Jew merely as another revolving wheel in the clock of progress, another factor in the development and advancement of medicine through the centuries. The science of medicine is universal and is the product of human thought and collective effort.

H.M.

COMMITTEE ON MATERNAL WELFARE

Eclampsia and Abruptio Placentae

A twenty-eight-year-old gravida III, para II, died in the thirty-second week of her third pregnancy. Both previous pregnancies had resulted in dead infants and had been complicated by hypertension.

No albumin was found in the first pregnancy, and the urinary findings were not recorded in the second. Nothing else is known of her past history regarding renal disease or hypertension. During the current pregnancy she had been seen only two or three times by her doctor, who never performed a urinalysis and who reported after death that "the blood pressure was not elevated."

At the thirty-second week she was admitted to the hospital with "labor pains" of ten hours' duration and a small show of blood. The blood pressure was 176 systolic, 110 diastolic. The fetal heart beat was absent. The urine was positive for albumin; the cervix was dilated sufficiently to admit one finger.

One and a quarter hours later, vomiting and profuse vaginal bleeding began, and a consultant was first called. He found her in clinical shock despite a blood pressure of 150 systolic, 80 diastolic.

With a transfusion running, hysterotomy was done, revealing a typical couvelaire uterus and dead fetus. Shock deepened but was corrected with further transfusion. Oliguria developed after operation, with a prolonged bleeding time and thrombocytopenia for five days. However, some urine was excreted daily. In the course of the next six days, the nonprotein nitrogen gradually rose to a high of 280 mg. per 100 cc., though the patient was afebrile and had been taking fluids by mouth. On the ninth day, however, acidosis became severe, resulting in a coma in which she died on the eleventh day.

Autopsy revealed typical findings of eclampsia and abruptio placentae, with focal glomerular scars representing older kidney lesions.

The preventability in this case was not considered, in view of the past history and evidence of severe previous kidney damage. However, the prenatal care was wholly inadequate, probably contributing substantially to the patient's death. In the first place, with the extremely bad obstetric history, there is grave doubt whether she should have been allowed to undertake a third pregnancy. Even assuming that she did so contrary to advice, difficulties should have been anticipated from the very start, and prenatal visits should have been made at weekly intervals from at least the second trimester. Actually, no urinalyses were recorded during the pregnancy. This is inexcusable. There is no evidence that the seriously depleted kidney function was assessed during prior pregnancies, before the onset of this one or, in fact, during this pregnancy. It is a notorious medical fact that women presenting this state of affairs frequently have serious toxemia of pregnancy as a superimposition of eclampsia on their already damaged renal function, and this seems not to have been anticipated. Once the catastrophe of toxic separation of the placenta had occurred, there is no quarrel with her treatment except that two hours were allowed to transpire between the time of admission and the time of consultation and cesarean section. Admittedly, the prognosis was so unfavorable from the start that little could have been done to alter the outcome. An interruption earlier in the pregnancy, preferably in the first trimester, might have prolonged this woman's life to a matter of years rather than months.

John Figgis Jewett, M.D.
Chairman

The following letter, which speaks for itself, has been received from the commander of the Boston Naval Shipyard.

> Doctor Robert W. Buck
> Secretary, Massachusetts Medical Society
> 22 Fenway
> Boston, Massachusetts
>
> Dear Doctor Buck:
>
> This Shipyard has at the present time a high sick leave rate that hurts the Shipyard in competition with other Shipyards in two ways; it increases our costs by adding this heavy burden to the overhead; and it deprives us of the productive effort of the employees who are out on sick leave. To combat the high overhead cost, the management of the Boston Naval Shipyard is waging a continuous war against unwarranted high costs. The purpose of this letter is to solicit your assistance in our fight against absenteeism; more specifically — the abuse of sick leave.
>
> Federal statutes permit a Civil Service worker to apply for sick leave benefits for absences due to sickness or injury *which physically incapacitate* him for the performance of his duties. Approval of a sick leave application depends on the evidence submitted to substantiate the need for the absence. For absence in excess of three days, the sick leave application must contain a physician's certification as to the earliest date the employee was able to return to duty. When abuse of sick privileges is suspected, such a certificate may be required for even one day of absence. In the absence of evidence to the contrary, the attending physician's certification is accepted as substantiation of the need for the employee's absence.
>
> I am not suggesting that any doctor advise his patient to return to work earlier than would be good for his health. However, it is my firm conviction that members of the medical profession can do a service to their profession, to their government and to themselves as taxpayers, by keeping in mind the following:
>
> (1) A sick leave application is a legal document which forms the basis for the payment of government funds;

(2) Each day of unnecessary and unwarranted absence contributes to excessive costs and delays in the timely completion of ships vitally needed by the Navy; and

(3) Unwarranted sick benefit payment, or padded or exaggerated vouchers, add to the tax burden of all citizens and, in addition, constitute an element of fraud.

Now the question is, what can your organization do to help? I believe the Officers of your association can help our campaign against high costs and unwarranted expenditure of public funds by:

(1) Giving wide publicity to the substance of this letter, and

(2) Supporting our plea for more critical attention to the medical certification on sick leave applications.

I would be very grateful if you could see your way clear to the publication of all or part of this letter in any magazine, newsletter, or other periodical which may be distributed to the members of your organization.

I want to emphasize again that I have no desire to withhold any sick leave benefits to which our employees are entitled. My sole aim in writing this letter is to explore every means I can find to help this Shipyard in its efforts to keep costs to an absolute minimum. Whatever you can do in furtherance of this aim would be very much appreciated, not only by the management of the Shipyard, but by the great majority of the employees who depend on the continued operation of the Shipyard for their livelihood. Thank you for any assistance you may be able to render.

Similar letters have been sent to the District Secretaries of the Massachusetts Medical Society.

Sincerely,

W. E. Howard, Jr.
Captain, USN
Commander

Robert W. Buck, M.D.
Secretary

CIVIL DEFENSE AGENCY

PLANS FOR THE PROVISION OF MORTUARY SERVICE IN LARGE-SCALE DISASTER

In the event of a small-scale disaster medical examiners of the Commonwealth could without undue difficulty cope with the many medicolegal problems related to identification and proper disposal of the dead. In a large-scale disaster, however, such as would occur in an attack without warning with atomic weapons, hundreds of thousands of fatalities could be expected, and the problems thus presented would be of great magnitude. Such a disaster could not be cared for by existing organizations, facilities and available personnel, and the mortuary service of civil defense, therefore, would begin operation.

Its functions would be as follows:

Organization and supervision of evacuation of dead from devastated areas, hospitals and casualty stations.

Establishment of supplementary mortuary facilities.

Identification of dead.

Filing of records of death in accordance with established legal routine.

Removal, identification, safekeeping and disposition of valuables from bodies, in accordance with established legal routine.

Supervision of movement of bodies to locations of burial from morgues.

Proper burial of claimed and unclaimed bodies.

Provision of appropriate religious representation at all burials.

In the event of evacuation of the general population the procedures would be the same as those that the Graves Registration Service of the Department of the Army has used for many years. Records are kept of local burying grounds, and redisposition of the remains can subsequently be made.

Mortuary services will be organized to correspond as much as possible to the districts of medical examiners. Each district should organize as much as possible an independent and self-sufficient mortuary unit capable of the disposal of the expected number of casualties. The chief of mortuary services in each district will be the medical examiner, who will have general supervision of the mortuary services within the district.

The chief of the district mortuary service along with his advisory staff should make the following provisions:

Collection of bodies from stricken areas in cooperation with casualty and rescue teams.

Transportation of bodies from stricken areas, hospitals and casualty stations to emergency morgues in co-operation with rescue, transportation and evacuation services.

Establishment, organization and operation of morgues.

Selection of emergency burial grounds, along with organization of personnel and plans for operating them.

Definition of basic procedures to be applied in caring for the dead in collection, in the morgue, and in burial under all forseeable circumstances.

Recruitment and training of personnel directly and indirectly related to the mortuary service.

Arrangement with neighboring districts for mutual aid.

Operational Plan

Scope of Organization

The size of an area and density of population should determine in a large measure whether a mortuary service should be organized on a full-scale basis; the need will be greatest in critical target areas. Districts, particularly cities, considered to be primary or

secondary target areas should organize on a full-scale basis, districts within a mutual aid zone organizing to provide supplementary mortuary services. The latter should organize sufficient personnel and equipment to form teams to be used in mobile support of stricken areas on call by the state director or area director of civil defense.

Field Collection Unit

The functions of the unit are as follows:

Organization of collection teams.

Supervision of the collection of bodies from stricken areas, hospitals and casualty stations.

Arrangement for prompt evacuation of bodies to morgues.

Organization is set up as follows:

The unit supervisor and his assistants should be responsible for the organization and carrying out of searching, collection and evacuation operations in accordance with a predetermined plan.

Collection teams. The responsibility for the prompt removal of bodies from the scene of disaster is that of the Rescue Service (*Rescue Manual* of the Massachusetts Civil Defense Agency). It is recognized that basic services to the living take precedence over services to the dead, and claims on specialized professional personnel in communities should be in keeping with local supply and the demands of the other services.

Field overseers should be well trained in observation, recognition and recording of significant identifying details and in the proper handling of bodies. They should be assigned to casualty teams, rescue teams, collection teams, casualty stations and hospitals. Their prime responsibility is to see that each body dispatched to a morgue has attached a tag containing as many required identifying data as can be obtained. Overseers working in the disaster area should supervise the activities of various personnel recovering and searching for bodies.

The operational plan in the disaster area should be as follows:

Before collection activities are initiated, the disaster area should be subdivided into sections and subsections demarcated by equally spaced concentric and radial borders, and reports should indicate the location to be free from dangerous radioactive contamination. An assistant supervisor of the collection unit should be placed in charge of each section, with the supervisor co-ordinating the activities of all the sections.

Each assistant supervisor should have assigned to him an adequate number of field overseers and vehicles. There should be approximately 1 field overseer for every 3 or 4 casualty, rescue or collection teams. The number of vehicles assigned will depend on their availability.

Beginning at the periphery, teams and vehicles should be dispatched in opposite directions from a central point in a subsection. These teams and vehicles should carry on operations until they meet those from an adjacent subsection, whereupon they should turn about and progress deeper into a section. In this way, the disaster area can be systematically combed.

Morgue Unit

The functions of the unit are as follows:

Identification of bodies along with completion and proper filing of records of death in accordance with established legal routine.

Carrying out of proper identification procedures for unidentified dead.

Preparation of official mortality lists.

Provision for the care of the property of the victims.

Arrangements for burial, including record of place.

The location and size of facilities should be as follows:

Morgues should be located as much as possible in existing facilities.

With an eye to minimizing transportation, auxiliary morgues can be established contiguous to hospitals and to burial places or cemeteries.

A minimal allowance of 32 square feet of floor space per body should be provided for.

Organization should be set up as follows:

A receiving team should consist of 3 persons: a supervisor to check tags and 2 assistants for handling and separating arriving bodies into specified groups. The number of receiving teams will depend on the morgue's capacity.

Processing teams should consist of 3 members each: a clerk and 2 processors working under direct supervision of a medical examiner. Persons with professional training in embalming, undertaking and so forth are exceptionally well qualified to serve on processing teams. Each team will be responsible for carrying out procedures recommended for processing dead bodies by the morgue unit. The number of processing teams will depend on the morgue's capacity.

An administrative and recording team is responsible for the making out of proper records, the keeping of valuables and the administration of the morgue. This team should consist of an administrative supervisor, a custodian of valuables and a supervisor of records, with an appropriate number of clerks and assistants to carry out their respective

responsibilities. The medical examiner should be in direct charge of the morgue unit, the administrative supervisor being next in line.

A public-care team should consist of police guards, information clerks, interviewers, escorts and the like.

A cemetery dispatching team should consist of 3 persons: a supervisor and 2 assistants. The supervisor should be responsible for the checking of each body to see if all necessary morgue procedures have been carried out and the body is ready for burial in an appropriately designated cemetery. The 2 assistants are assigned to handling of bodies and loading them for transportation to the cemetery or burial grounds.

A typical morgue unit based on the ability of a medical examiner to handle 500 bodies within a day or two should consist of the personnel listed in Table 1.

TABLE 1. *Personnel of a Typical Morgue Unit.*

DESCRIPTION		NO. OF PERSONNEL
Receiving teams (2 or 3 persons each)	—	6
Processing team	—	16
Medical examiner in charge	1	—
Clerk & 2 processors (5 teams)	15	—
Administrative & recording team	—	14
Administrative supervisor	1	—
Assistants for maintenance & various general duties	6	—
Custodian of valuables	1	—
Clerk	1	—
Assistant	1	—
Supervisor of recording	1	—
Clerks	3	—
Public-care team	—	18
Police guards with supervisor	6	—
Visitor escorts	6	—
Information clerks & interviewers	6	—
Cemetery dispatching teams (2 or 3 persons each)	—	6
Total		60

Burial or Cemetery Unit

The facilities of the unit should be as follows:

Each area should examine the capacities and locations of its cemeteries. Supplemental burying grounds should be designated and planned according to estimates of expected casualties. Emergency cemetery or burial grounds should be selected with the following considerations in mind: conservation of transportation, difficulties of excavation, drainage, distance from water reserves, dangers of contamination, availability of electric power and legal restrictions.

Estimates and arrangements for procurement of equipment needed in grave preparation should be made with the rescue, transportation and evacuation service.

The functions of the unit are as follows:

Preparation of graves.
Burial.
Grave registration.

MOBILIZATION

Personnel

The civil-defense mortuary service should, so far as possible and practicable, be built around existing professional mortuary personnel. Lay volunteers should be used whenever and wherever possible. Selection of qualified personnel for the operation of mortuary services should be the responsibility of the chief of the district mortuary service.

Training

The district chief should be responsible for the training of Mortuary Service personnel. In addition, training should be provided for personnel of casualty and rescue team, particularly in observation and recording of valuable identifying data.

Transportation

Each morgue and burial or cemetery unit should have certain vehicles assigned to it from the transportation service, preferably light enclosed trucks, for carrying supplies to morgues and cemeteries, for collection of bodies and movement of them to morgues and cemeteries, and for transporting property removed from bodies and records to designated permanent custodial facilities. The number of vehicles needed should be estimated on the basis of expected casualties. Personnel for their operation should be provided by the transportation service.

Supplies

The supplies most essential to a mortuary operation are forms necessary for identification and record procedures. These forms will be standard and will be provided by the Civil Defense Agency. Other supplies, such as body containers, housekeeping and office supplies, and technical equipment will be provided as available. Past experience of the military has conclusively demonstrated that the most reliable and practical method available for identifying the dead is to provide the living with some indestructible means of recognition, such as metal identification tags. It is to be noted that if the particulars on a motor-vehicle license were engraved on a stainless-steel plate, it would prove a most valuable method of identification. Without indestructible identification tags chances of success in identifying a large number of bodies resulting from a catastrophe would be slight.

RICHARD FORD, M.D.
Chief, Mortuary Service

THOMAS F. MAHER, M.D., D.P.H.
Executive Medical Officer

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1955

RÉSUMÉ

Disease	Oct. 1955	Oct. 1954	Seven-Year Median
Chancroid	0	0	2
Chicken pox	277	254	307
Diphtheria	2	3	9
Dog bite	1023	1193	936
Dysentery, bacillary	32	9	15
Encephalitis, infectious	2	4	2
German measles	38	59	54
Gonorrhea	176	227	239
Granuloma inguinale	0	0	0
Hepatitis, infectious	34	77	39*
Lymphogranuloma venereum	1	1	0
Malaria	0	0	1
Measles	27	969	126
Meningitis, meningococcal	5	2	6
Meningitis, Pfeiffer bacillus	2	2	1
Meningitis, pneumococcal	0	1	1
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	1	0	0
Meningitis, undetermined	9	16	7
Mumps	89	404	404
Poliomyelitis	476	245	123
Salmonellosis	23	23	14
Scarlet fever	110	117	127
Syphilis	182	109	141
Trichinosis	3	0	2
Tuberculosis, pulmonary	137	198	152
Tuberculosis, other forms	11	11	9
Typhoid fever	1	1	2
Undulant fever	0	0	2
Whooping cough	77	213	213

*Six-year median.

Comment

Diseases below the seven-year median were chicken pox, diphtheria, German measles, infectious hepatitis, measles, mumps, scarlet fever and whooping cough.

Only 34 cases of infectious hepatitis were reported during October. Not only is this the lowest figure for this disease for the month of October since 1951, it also (with August, 1955, included) is the lowest figure for any month since July, 1952.

With but one exception (October, 1953) the figure for measles represents the lowest figure for this disease for the month of October in the State's history.

During October mumps was at the lowest level for this month since 1925.

With but one exception (October, 1953) scarlet fever was at the lowest level during October than for the corresponding month in the history of the State.

By a considerable margin whooping cough during the month of October reached the lowest level for this month in the State's history.

Diseases above the seven-year median were bacillary dysentery, poliomyelitis and salmonellosis.

During October poliomyelitis was at the highest level for this month since 1916.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Anthrax: Haverhill, 1.

Diphtheria: Boston, 2.

Dysentery, amebic: Northampton, 1.

Dysentery, bacillary: Belmont, 1; Boston, 7; Fitchburg, 1; Lowell, 1; Waltham, 15; Worcester, 7; total, 32.

Encephalitis, infectious: Boston, 1; Waltham, 1; total, 2.

Hepatitis, infectious: Billerica, 1; Boston, 2; Cambridge, 1; Chelmsford, 1; Chelsea Naval Hospital, 6; Fort Devens, 3; Gloucester, 1; Haverhill, 2; Hopkinton, 3; Lowell, 2; Ludlow, 3; Lynn, 1; Newton, 2; Provincetown, 1; Springfield, 2; Wenham, 2; Westford, 1; total, 34.

Lymphocytic choriomeningitis: Worcester, 1.

Meningitis, meningococcal: Boston, 1; Cambridge, 1; Waltham, 1; Weymouth, 1; Worcester, 1; total, 5.

Meningitis, Pfeiffer bacillus: Chicopee, 1; Worcester, 1; total, 2.

Meningitis, streptococcal: Southbridge, 1.

Meningitis, undetermined: Barre, 1; Boston, 1; Cambridge, 1; Natick, 1; Pittsfield, 1; Randolph, 1; Richmond, 1; Springfield, 1; Worcester, 1; total, 9.

Meningitis, *Escherichia coli:* Worcester, 1.

Poliomyelitis: Abington, 1; Acton, 1; Amherst, 1; Andover, 1; Arlington, 9; Ashland, 4; Attleboro, 5; Barnstable, 2; Barre, 3; Bedford, 3; Bellingham, 1; Belmont, 1; Beverly, 3; Billerica, 3; Blackstone, 1; Boston, 44; Braintree, 1; Bridgewater, 3; Brockton, 1; Brookline, 2; Burlington, 5; Cambridge, 17; Canton, 1; Carver, 1; Chatham, 2; Chelsea, 6; Chesterfield, 1; Chicopee, 2; Clinton, 5; Concord, 2; Cummington, 1; Danvers, 3; Dartmouth, 2; Dedham, 3; Dennis, 1; Douglas, 1; Dover, 1; Dudley, 1; Duxbury, 3; East Bridgewater, 1; Easthampton, 2; Edgartown, 1; Everett, 4; Fall River, 3; Falmouth, 5; Framingham, 10; Franklin, 1; Gardner, 1; Georgetown, 1; Great Barrington, 1; Hamilton, 1; Harwich, 2; Haverhill, 2; Hingham, 1; Holbrook, 1; Holden, 1; Hopkinton, 1; Hull, 1; Kingston, 2; Leicester, 1; Leominster, 3; Lexington, 3; Lincoln, 2; Lynn, 14; Lynnfield, 2; Malden, 5; Marblehead, 4; Maynard, 1; Medford, 11; Melrose, 2; Mendon, 1; Milford, 5; Millbury, 1; Millis, 2; Milton, 2; Montague, 1; Nantucket, 2; Natick, 1; Needham, 5; New Bedford, 6; Newburyport, 1; Newton, 16; Norfolk, 1; North Adams, 1; North Andover, 1; North Reading, 1; Northboro, 1; Northbridge, 2; Norwell, 1; Norwood, 5; Oak Bluffs, 1; Oxford, 2; Peabody, 5; Pepperell, 1; Pittsfield, 3; Plymouth, 3; Plympton, 1; Quincy, 13; Randolph, 5; Reading, 2; Revere, 4; Richmond, 1; Salem, 5; Saugus, 4; Scituate, 2; Sharon, 1; Somerville, 9; Southboro, 1; Springfield, 10; Stoneham, 2; Stoughton, 2; Stow, 2; Swampscott, 6; Templeton, 2; Tewksbury, 2; Tewksbury State Infirmary, 1; Upton, 5; Wakefield, 3; Walpole, 1; Waltham, 9; Warren, 1; Watertown, 1; Wellesley, 9; Wenham, 2; West Boylston, 2; West Springfield, 2; Westfield, 1; Westover Field, 5; Westport, 1; Westwood, 2; Weymouth, 11; Whitman, 1; Williamstown, 3; Wilmington, 1; Winthrop, 11; Woburn, 5; Worcester, 13; Worthington, 1; Wrentham, 1; Yarmouth, 1; total, 476.

Salmonellosis: Boston, 6; Cambridge, 1; Lawrence, 1; Leominster, 2; Lexington, 1; Lowell, 1; Marion, 1; Newton, 1; Revere, 2; Rockland, 1; Springfield, 2; Stoughton, 1; Waltham, 2; Worcester, 1; total, 23.

Trichinosis: Boston, 1; Chicopee, 2; total, 3.

Typhoid fever: Worcester, 1.

CORRESPONDENCE

SALK VACCINE AND PENICILLIN SENSITIVITY

To the Editor: I am writing about the penicillin content in the Salk poliomyelitis vaccine, penicillin and streptomycin having been included in the vaccine to guard against bacterial contamination. Polymyxin has been proved and accepted as a suitable substitute, and poliomyelitis vaccine released in the future by one of the six companies authorized in its production will contain polymyxin in place of penicillin.

Owing to the small number of children reacting to the Salk poliomyelitis vaccine in the 1954 evaluation report on the field test, Drs. Salk, Francis, Siegel and Workman came to the conclusion: "The vaccine should offer no hazard either to patients allergic to penicillin or as a source of newly acquired penicillin sensitization."

My concern is not with the number of allergic or sensitized children with poison ivy who react to the Salk vaccine, but with the hundreds of thousands and millions who have had and will receive the vaccine who have never had penicillin or streptomycin in any shape or form. If they are sensitized there will be no reaction from the vaccine at the time given; their sensitization will not be determined unless in later life the use of penicillin is indicated and given.

Letters were mailed to certain members of the medical profession, including those closely associated with the development and direction of the process of the production of the Salk poliomyelitis vaccine, asking for proof that sensitization to penicillin and horse serum was comparable. No proof or evidence has been obtainable, but the following observations suggest that sensitization to penicillin and horse serum are comparable.

In the early days of immunization, before the days of tetanus toxoid, when children were immunized against diphtheria a small amount of horse serum in the form of antitoxin was added to the toxin-antitoxin mixture. The amount of penicillin added to the Salk vaccine is com-

parable to the 0.8 cc. of antitoxin added to 35,000 cc. of the toxin-antitoxin mixture. Sheep or goat serum was substituted for horse serum in later manufacture of the toxin-antitoxin mixture, and penicillin has replaced horse serum as the most common cause of death from anaphylactic shock.

The medical profession and Government officials having so much to do with appropriation of funds to be used in the free distribution of the vaccine should be informed of these facts, and they should not only recommend but demand that the other five companies authorized to produce the vaccine be required to substitute polymyxin for penicillin, instead of allowing them to rely on their own judgment whether they continue the production of the vaccine as at present, or substitute other antibiotics at their discretion, when polymyxin has been proved and accepted as a suitable substitute.

More than 14,000,000 children in the United States alone have already received the Salk vaccine with the penicillin content, and every person under the age of twenty, including pregnant women and very young children, is being urged to take the vaccine as soon as it is available.

If the public realizes that certain children are unnecessarily being made vulnerable to the use of penicillin, the antibiotic most responsible for revolutionizing the practice of medicine, and further loses faith in the vaccine, its usefulness will be restricted, and for many persons it will be a total loss.

C. C. McLean, M.D.

Birmingham, Alabama

NOTICES

NEW ENGLAND ROENTGEN RAY SOCIETY

The monthly meeting of the New England Roentgen Ray Society will be held at the Hotel Commander, Cambridge, Massachusetts, on Friday, December 16.

PROGRAM

4:30 p.m. Film-reading session.
5:45 p.m. Business meeting.
6:00 p.m. Dinner.
8:00 p.m. Roentgen Image Amplification. Dr. Russell Morgan, of Baltimore.

AMERICAN COLLEGE OF CHEST PHYSICIANS AND OVERHOLT THORACIC CLINIC

A meeting of the New England States Chapter of the American College of Chest Physicians and the Overholt Thoracic Clinic will be held in the Joslin Auditorium, New England Deaconess Hospital, on Wednesday, December 21, at 4 p.m. Dr. Paul D. White will speak on the subject "Prognosis in Coronary-Artery Disease."

SOCIETY MEETINGS AND CONFERENCES

December 8–14, 1955, and January 30–February 8, March 19–28 and June 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

December 8–28. Consultation Clinics for Crippled Children in Massachusetts. Page 937, issue of November 24.

December 9 and 10. Association for Research in Nervous and Mental Disease. Page 745, issue of October 27.

December 13 and 20. Boston City Hospital House Officers' Association. Page 793, issue of November 3.

December 14, 1955, and February 15, March 28 and April 18, 1956. Greater Boston Medical Society. Page 208, issue of August 4.

December 15. Arthritis Study Unit, Page 668, issue of October 13.

December 16. New England Roentgen Ray Society. Notice above.

December 21. American College of Chest Physicians and Overholt Thoracic Clinic. Notice above.

January 9–14, 1956. Pan American Congress of Ophthalmology. Page 944, issue of November 24.

January 16, 1956. Hartford Medical Society. Page 708, issue of October 20.

January 16, February 6, March 5 and April 2, 1956. Fried Lecture Series. Page 535, issue of September 22.

January 20–27, 1956. Fifth Panamerican Congress of Gastroenterology. Page 746, issue of October 27.

January 25, February 29, March 21 and April 25, 1956. Massachusetts Heart Association. Page 623, issue of October 16.

January 25, March 21 and April 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

March 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.

May 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.

May 3–5, 1956. American Goiter Association. Page 348, issue of August 25.

May 28–June 1, 1956. European Symposium on Vitamin B. Page 578, issue of September 29.

June 21–24, 1956. American Academy of Dental Medicine. Page 994, issue of December 1.

August 19–23, 1956. American College of Chest Physicians. Page 840, issue of November 10.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 15

THURSDAY, DECEMBER 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Guest Speaker of the Bingham Association. Hemorrhagic Disorders. Dr. Edwin W. Campbell. Stearns Auditorium, New England Center Hospital.
11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m.–12:00 m. Thoracic Conference. Further Follow-up Reports on Patients with Mitral Stenosis. Drs. Laurence B. Ellis and Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.
*12:00 m. Staff Conference. Dr. Robert E. Gross. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*4:00 p.m. Guest Speaker of the Bingham Association. Allergy and Vasculitis. Dr. Robert P. McCombs. Stearns Auditorium, New England Center Hospital.

FRIDAY, DECEMBER 16

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*7:30–9:30 p.m. Postgraduate Medical Institute. Sedatives, Hypnotic and Tranquillizing Agents. Drs. Friend and Knapp. Holyoke Soldiers' Home, Holyoke.

SATURDAY, DECEMBER 17

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, DECEMBER 19

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. William Schwartz. Stearns Auditorium, New England Center Hospital.

(Concluded on page xxxi)

METAMUCIL® IN BOWEL MANAGEMENT

"Smoothage-Bulk" Restores Normal Peristalsis

The gentle distention of the bowel wall provided by Metamucil® is physiologically corrective in constipation management.

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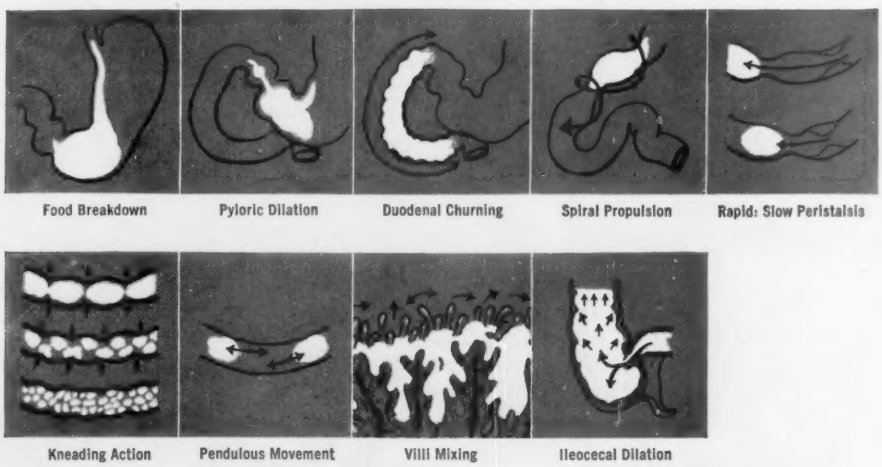

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(Additional advertisements on page xxvi)

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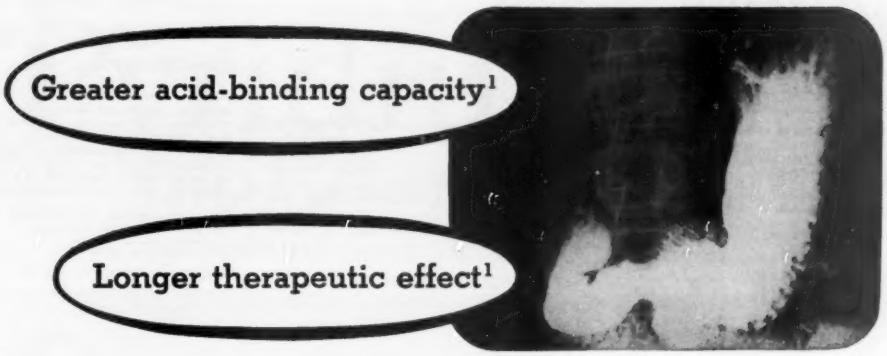

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1. Rossett, N.E., Rice, M.L. Jr.: An In Vitro Evaluation of the More Frequently Used Antacids, Gastroenterology 26:490 (1954).

2. Morrison, Samuel: Magnesium Aluminum Hydroxide Gel in the Antacid Therapy of Peptic Ulcer, Am. J. Gastroenterology 22:309 (1954).

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(Additional advertisements on page xxii)

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SHARP & DOHME
Philadelphia 1, Pa.
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REFERENCE: 1. Kirwin, T. J., Lowsley, O. S., and Menning, J., *Am. J. Surg.* **62**:330-335, December 1943.

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MAJOR ADVANTAGES: Easy-to-give. Tablets dissolve readily in water, milk, fruit juices, infant formulas.

Six dosage strengths of PENALEV give you true flexibility of dosage wherever oral penicillin is indicated. Side reactions are less frequent than with injections.

Supplied: Soluble *Tablets* of 50,000, 100,000, 200,000, 250,000, 500,000 or 1,000,000 units of potassium penicillin G. Ideally suited to pediatrics, prescription compounding, aerosol therapy.

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Products Born of Continuous Research
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(Concluded from page 1048)

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Curare and Curare-like Agents. Dr. Lipschitz. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward H. MacMahon. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference of Greater Boston. Panel Discussion — Endotracheal Technics. Dr. Smith. Auditorium, Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

TUESDAY, DECEMBER 20

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Guest Speaker of the Bingham Associates. Fluids and Electrolytes. Dr. Gerald D. Aronson. Stearns Auditorium, New England Center Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
°2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
°5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. Current Concepts of the Sprue Syndrome. Dr. Chester M. Jones. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, DECEMBER 21

Greater Boston Medical Society (dinner meeting). Dr. Jack Ewalt, speaker. Hotel Fensgate, 534 Beacon Street, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Old Age as a Public Health Problem. Dr. Claire Ryder, Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. Bertram Selverstone, John F. Sullivan and Justin Hope. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Surgical Pathology Conference. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
°4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
°6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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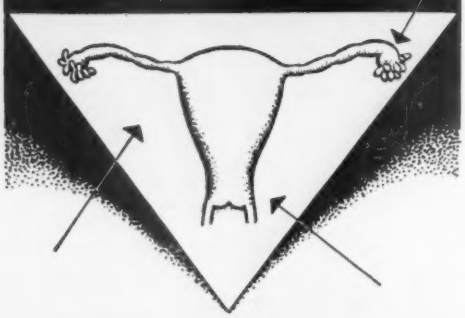

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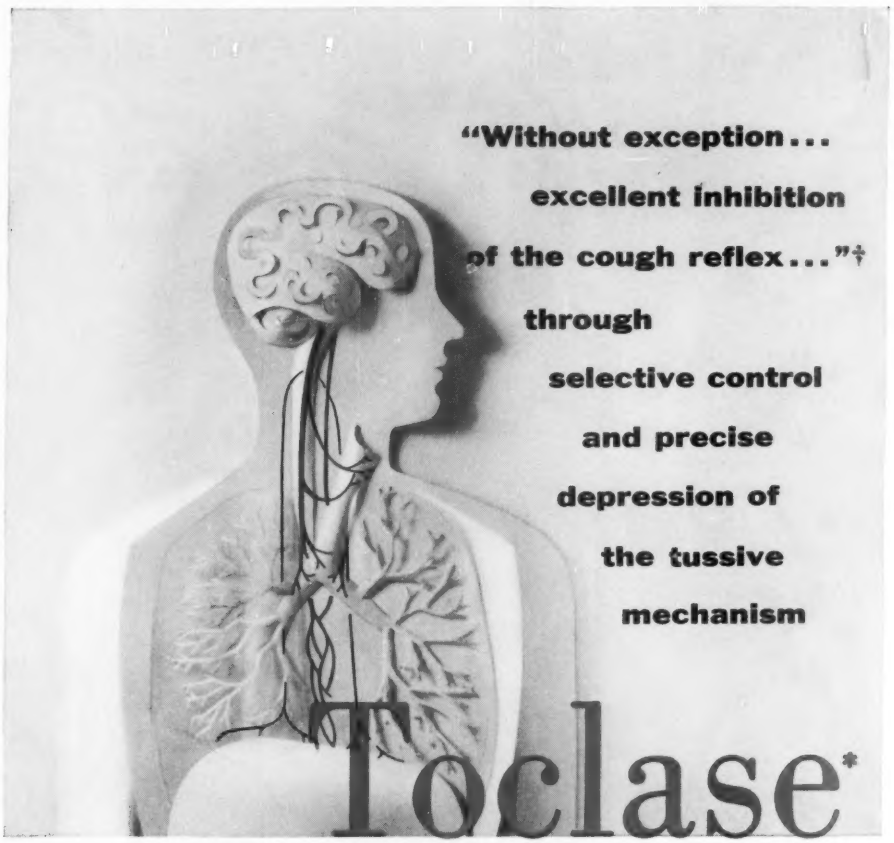
Index to Advertisers

	PAGE
Ames Company, Inc.	iv
The Armour Laboratories	xxxii
Ayerst Laboratories	xiv
Baldpate, Inc.	xxvi
John A. Baleno, R. P. T.	xxii
Boston Medical Laboratory	xxii
Bristol-Myers Co.	xii
Central Pharmacal Company	xxx
Ciba Pharmaceutical Products, Inc.	xx, xxi, Back Cover
David Memorial Nursing Home	xxvi
Electroencephalographic Laboratory, Inc.	xxii
Glenside, Inc.	xxvi
Hanover House, Inc.	xxvi
Hoffman-La Roche, Inc.	After xii
Chas. B. Knox Gelatine Co., Inc.	v
Lakeside Laboratories, Inc.	viii
Leary Laboratory	xxii
Lederle Laboratories	xiii
Thos. Leeming & Co., Inc.	xxxi
Eli Lilly and Company	xviii
Medical Clearing Bureau, Inc.	xx
Metropolitan Travel Service, Inc.	xxi
T. J. Noonan Co.	xxi
Nuclear Instrument and Chemical Corporation	x
Parke, Davis and Company	ii, iii
Perkins School	xxvi
Pfizer Laboratories (Div. of Chas. Pfizer & Co., Inc.)	vii, xxxiii
Ring Sanatorium	xxvi
Wm. H. Rorer, Inc.	xxv
Sandoz Pharmaceuticals	xxiv
W. B. Saunders Company	Front Cover
Schering Corporation	xv
Julius Schmid, Inc.	vi
G. D. Searle and Company	xix
Sharp & Dohme (Div. of Merck & Co., Inc.)	xxvii, xxix
Smith, Kline & French Laboratories	xi
E. R. Squibb & Sons (Div. of Mathieson Chemical Corporation)	ix
Storrow House (Massachusetts General Hospital)	xxvi
Tweeds, Limited	xxviii
United States Brewers Foundation	xvi
Washingtonian Hospital	xx
J. S. Waterman & Sons	xx
Wiswall Sanatorium	xxvi
Woodside Cottages, Inc.	xxvi
Wyeth Laboratories	xvii



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